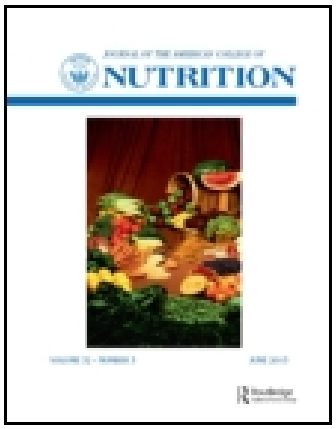

Journal of the American College of Nutrition
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/uacn20

Hypothesis: dietary management may improve survival from nutritionally linked cancers based on analysis of representative cases.

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Published online: 02 Sep 2013.

To cite this article: J P Carter, G P Saxe, V Newbold, C E Peres, R J Campeau & L Bernal-Green (1993) Hypothesis: dietary management may improve survival from nutritionally linked cancers based on analysis of representative cases., Journal of the American College of Nutrition, 12:3, 209-226, DOI: 10.1080/07315724.1993.10718303

To link to this article: http://dx.doi.org/10.1080/07315724.1993.10718303

Hypothesis: Dietary Management May Improve Survival from Nutritionally Linked Cancers Based on Analysis of Representative Cases

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Key words: diet, macrobiotic, pancreatic cancer, prostate cancer, outcome, survival, quality of life

A limited number of case histories was analyzed and verified to examine the effect of a very low fat, moderately high fiber, and moderately reduced calorie diet on the survival and quality of life of patients with primary cancer of the pancreas, metastatic stage D2 prostate cancer, and other nutritionally linked cancers. The retrospective study of pancreatic cancer patients disclosed that 1-year survival was higher among those who modified their diets than in those for whom there was no evidence as to diet alteration. For patients with metastatic prostate cancer (stage D2), a case control study demonstrated a statistical association of dietary modification with longer survival and improved quality of life. A retrospective study utilizing questionnaires supported such dietary modifications as a useful tool in the management of nutritionally linked cancers.

Abbreviations: CT = computerized axial tomography, RR = relative risk, SEER = Surveillance Epidemiology and End Results

INTRODUCTION

A dietary pattern high in fat, calories, and animal protein, and low in cereal fiber, carotenoids, selenium, and omega-3 fatty acids (as is common in the West), is suspected, on the basis of epidemiologic [1–4], metabolic [5–7], animal [8–10], and cell-culture [11,12] studies, of playing a role in the etiology of a number of cancers. Nutritionally linked cancers include: colorectal [13], breast [14], uterine [15], ovarian [15], prostatic [16], and pancreatic [9]. Lung cancer, mainly smoking related, may also have a nutritional component [17]. Several recent studies have associated breast cancer and high fat intake with poor prognostic indications (low estrogen receptor levels and advanced tumor stage) [18] and decreased survival [19,20]. Risk of breast cancer has been inversely associated with fiber intake [21]. Based on information from animal experiments [9,11,14], the primary nutritional risk factor is thought to be total fat intake (saturated and polyunsaturated fatty acids).

Carcinogenesis is widely conceived as a two-step or multi-step process incorporating both initiation and promotion phases. While the initiation phase is considered to consist of irreversible somatic mutation, the subsequent promotion phase may be at least partly reversible [22]. It is during this promotion phase that dietary modification may have its greatest potential to modify carcinogenesis.

A macrobiotic dietary approach is among the most popular unconventional approaches used by cancer patients in the United States to treat illness and pathology caused by progression of an invasive neoplasm [23,24]. It does not alleviate the side effects of cancer chemotherapy and/or radiation therapy nor will it prevent advancement to metastatic disease and cachexia, that is associated with increased metabolic rate and increased energy expenditure. The latter is mediated through gluconeogenesis and futile cycles, heat generating processes, which are associated with increased levels of tumor necrosis factor, endotoxin, and

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Journal of the American College of Nutrition, Vol. 12, No. 3, 209–226 (1993)
Published by the American College of Nutrition

an increase in acute phase reactants. This condition can be treated by conventional nutritional support.

The dietary approach that has been termed "macrobiotic" includes reduced consumption of meat and dairy products and increased consumption of cereal grains, legumes, cruciferous and other dark green and deep yellow vegetables. The antineoplastic effects of these products may be mediated by reducing intake of diet-borne tumor promoters or, directly, by providing anti-tumor-promoting factors [20,25]. Moderately reduced caloric intake and increased intake of antioxidants and fiber may have protective effects over time [20,25]. Such changes may inhibit and perhaps reverse tumor development and thereby contribute to an increase in overall survival [26]. Dietary modification may therefore be a useful tool in the management of nutritionally linked cancers.

The mechanisms involved in nutritionally linked cancers may have multi-effector elements, including hormonal imbalance resulting from increased synthesis of estrogen by the adrenal gland, and/or fat cells; biosynthesis of serum hormone-binding globulin or bile acids; and membrane and intracellular changes. The amount of monounsaturated olive oil, omega-3 polyunsaturated (fish) oils, and medium-chain triglycerides consumed does not further the development of these cancers, possibly because they have a neutral action or a protective effect in host metabolism [27].

Contrary to theoretical analyses by critics [8], a properly planned, macrobiotic diet can usually meet both the Recommended Dietary Allowances for essential nutrients (including vitamin B_{12}) [28,29] and the cancer dietary guidelines of the National Research Council [2]. During critical growth periods, such as childhood, adolescence, and pregnancy, the standard macrobiotic diet provides marginally adequate nutrients [30]. The diet suggested for cancer patients is a modified standard macrobiotic diet composed of approximately 50–60% whole cereal grains, 25% vegetables, 15% beans and sea vegetables, and 5% miso soup. Supplementary foods, such as sweets and condiments, are not recommended. (Fish is allowed in the standard macrobiotic diet.) The macrobiotic plan is, on the average, 30% lower in total fat. Patients in the studies described adopted this dietary pattern to varying degrees.

Table 1. Contingency Table of One-Year Survival in Primary Pancreatic Cancer

	Alive	Dead	Total
Dietary modification	12	11	23
No dietary modification (SEER)	142	1325	1467

SEER = Surveillance Epidemiology and End Results

In three separate studies of cancer patients who adopted a modified macrobiotic diet, we examined survival and disease status, focusing on: 1) primary pancreatic cancer; 2) metastatic (stage D2) prostate cancer; and 3) miscellaneous cancers reported in questionnaires filled out by patients. Results of these studies are presented here in order to explore the relation of modified macrobiotic diet plans for cancer patients and the effects on length and quality of survival and overall median survival rates.

MATERIALS AND METHODS

Pancreatic

The study sampling frame consisted of 101 patients diagnosed with primary adenocarcinoma of the pancreas who had received macrobiotic dietary counseling from January 1980 through June 1984 from a certified counselor listed in a directory provided by the East West Foundation

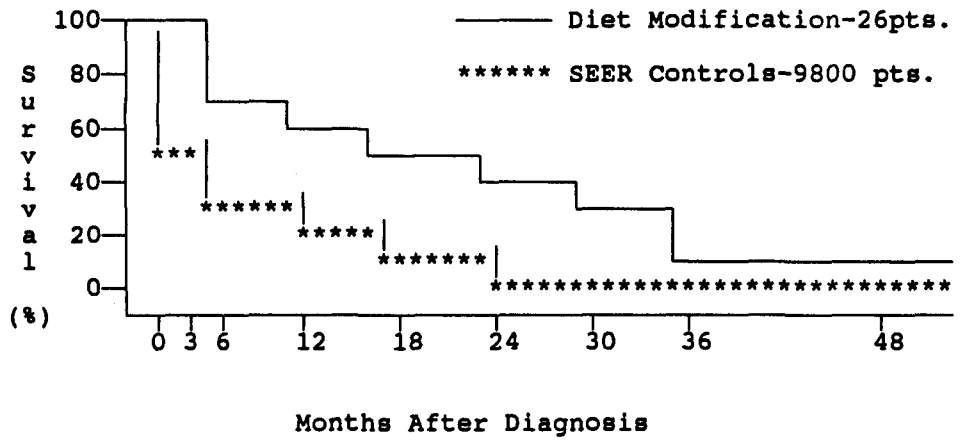

Fig. 1. Comparison of survival times of pancreatic cancer patients who adopted macrobiotic diet to those that did not change their diet.

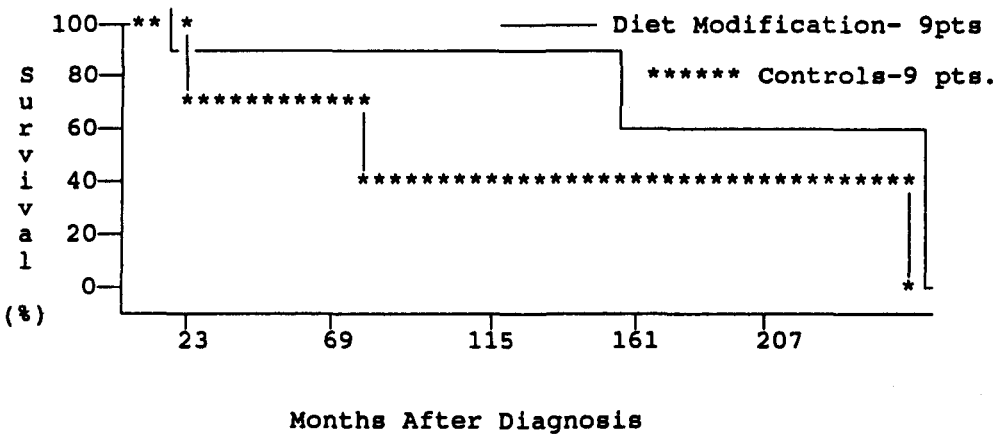

Fig. 2. Comparison of survival times of nine (stage D2) prostate cancer patients who adopted macrobiotic diet, to nine controls who did not change their diet.

(Brookline, MA). These patients did not have any surgical treatment of their pancreatic cancer.

Of 101 patients identified, only 28 were located, 23 of whom had changed their diet to at least a moderate extent. This study sample followed a modified macrobiotic diet for at least 3 months reported by the patients or next-of-kin for the 16 who died by time of contact. The 3-month dietary period was selected as a compromise between: 1) the minimum amount of time, according to practitioners, which would be required to see an effect of dietary modification on disease status [31]; and 2) the maximum amount of time most patients were likely, in our judgment, to stay on the diet without outside reinforcement. Pathological confirmation, date of diagnosis and death were obtained, when possible, from the subject's physician or hospital medical records. If medical records and/or pathology reports could not be obtained, confirmation of the disease site, stage and date of diagnosis and death was asked of the patient or next-of-kin. Medical records and/or reports from patient or next-of-kin indicated that only in one case was the disease confined to the pancreas.

Controls consisted of 1,467 pancreatic adenocarcinoma cases from the SEER (Surveillance Epidemiology and End Results) National Tumor Registry who had regional or distant disease and who were diagnosed during the same time period. No information is available as to pre- or postdiagnosis diet of those in the control population. Anorexia is probable in at least some of the controls. Of the 1,467 patients, 1,325 died.

Prostate

The sample for this study consisted of 18 patients diagnosed with stage D2 prostate cancer, 9 of whom adopted a macrobiotic diet, to a great or moderate extent, as adjunctive therapy. Four had an orchiectomy performed, 3 had both radiation therapy and hormonal therapy, 2 had orchiectomy and hormonal or radiation therapy, and 1 had Flutamide and Leuprolide. Three of the patients had long-term (5 years) healing or regression of bone lesions.

Nine controls (matched according to age, Gleason score, and type of treatment) were identified from both Tulane University Hospital and Clinic tumor registry and Pendleton Memorial Methodist Hospital tumor registry. Socioeconomic status of the two groups was comparable, and since our controls were identified from private hospitals, we can assume that they belong to the middle to upper socioeconomic classes.

Other Cancers

A retrospective study was conducted in 1989, using a nationwide mail survey. The 182 study subjects were male and female cancer patients 34–78 years of age at the time of diagnosis, and diagnosed with histologically confirmed primary or secondary invasive cancer during the period 1980–1989. All of whom had sought macrobiotic counseling. Information on demographic characteristics, familial medical history, smoking and dietary habits was collected through the use of a questionnaire. Data were analyzed to determine survival length and quality of life. No controls were used.

Table 2. Contingency Table of Survival in (Stage D2) Prostate Cancer

	Alive	Dead	Total
Dietary modification	6	3	9
No dietary modification	5	4	9

Table 3. Gleason Score Comparisons, Regression (Healing), and Progression-Free Survival in Stage D2 Prostate Cancer Patients Following Macrobiotic and Standard American Diets

Macrobiotic diet	Standard American diet
Low fat (10–12%)	High fat (40%)
Long-term healing of multiple bone lesions in three cases.	No regression or healing. (At best there was transient improvement in bone lesions with orchiectomy or estrogen therapy.)
Gleason scores of 7 or less were not progressive. Cases were not progressive until surgical trauma, stress, or until patient began to deviate from the diet.	Gleason scores of 4 or less were not progressive.
100% had long-term (5 years) survival free of progression, before diet deviations began.	61% had survival free of progression (followed for 94 months).
Median survival = 228 months	Median survival = 45 months

RESULTS

In the pancreatic cancer study design several demographic differences between cases and controls were observed. Cases (mean age at diagnosis = 63.9) were younger than SEER controls (mean age = 67.9), had a greater preponderance of males (53.8 vs 50.1%), and had a slightly different racial composition. (Cases were 84.6% white/15.4% black; controls were 75.7% white/24.1% black/0.2% "other.") None of these differences would be expected to have major prognostic significance.

Survival analyses are based on those 23 patients who reported at least a moderate degree of dietary modification. Mean length of survival in the 23 patients was 17 months, compared with 6 months for the SEER controls. Median survival was 13 vs 3 months for SEER. The 1-year survival rate was 52% in the diet group (12/23) vs 9.7% (142/1467) for SEER ($p < 0.0001$). Relative risk (RR) for 1-year survival = 5.38 (Miettinen test-based 95%, CI = 3.28, 8.84) (Fig. 1, Table 1).

Survival analyses for the prostate cancer study are based on 18 prostate cancer patients. Mean length of survival among patients who changed their diet was 177 months, with median survival of 228 months, compared to controls whose mean length of survival was 91 months, with median survival of 72 months. The odds ratio was 1.6 with

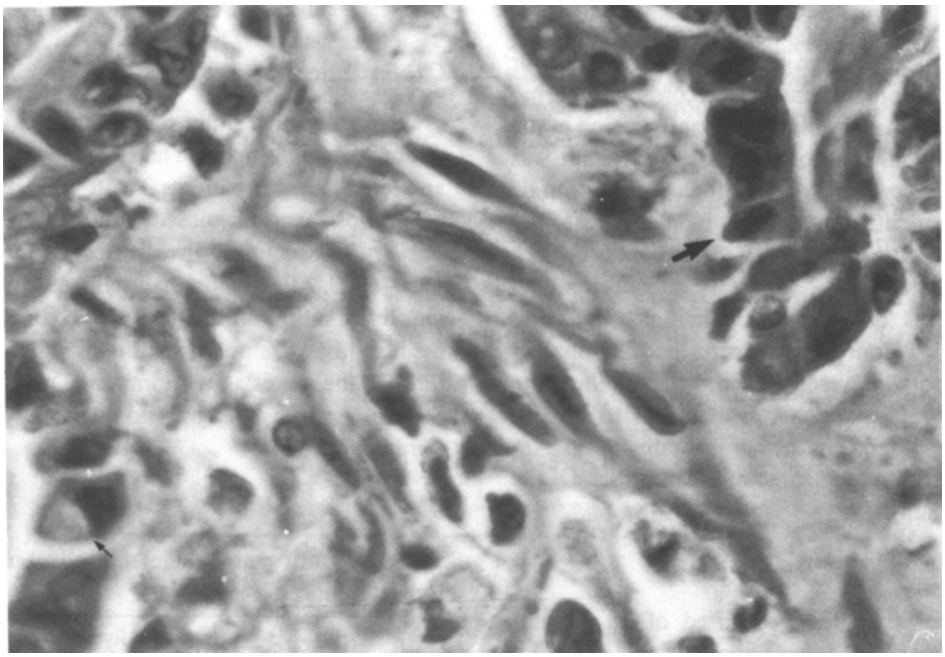

Fig. 3. Case No. 1. Section of duodenal wall showing infiltrative adenocarcinoma. Well-differentiated glandular structure is seen (large arrow). Tumor also shows signet ring-type single cells (small arrow) (×400).

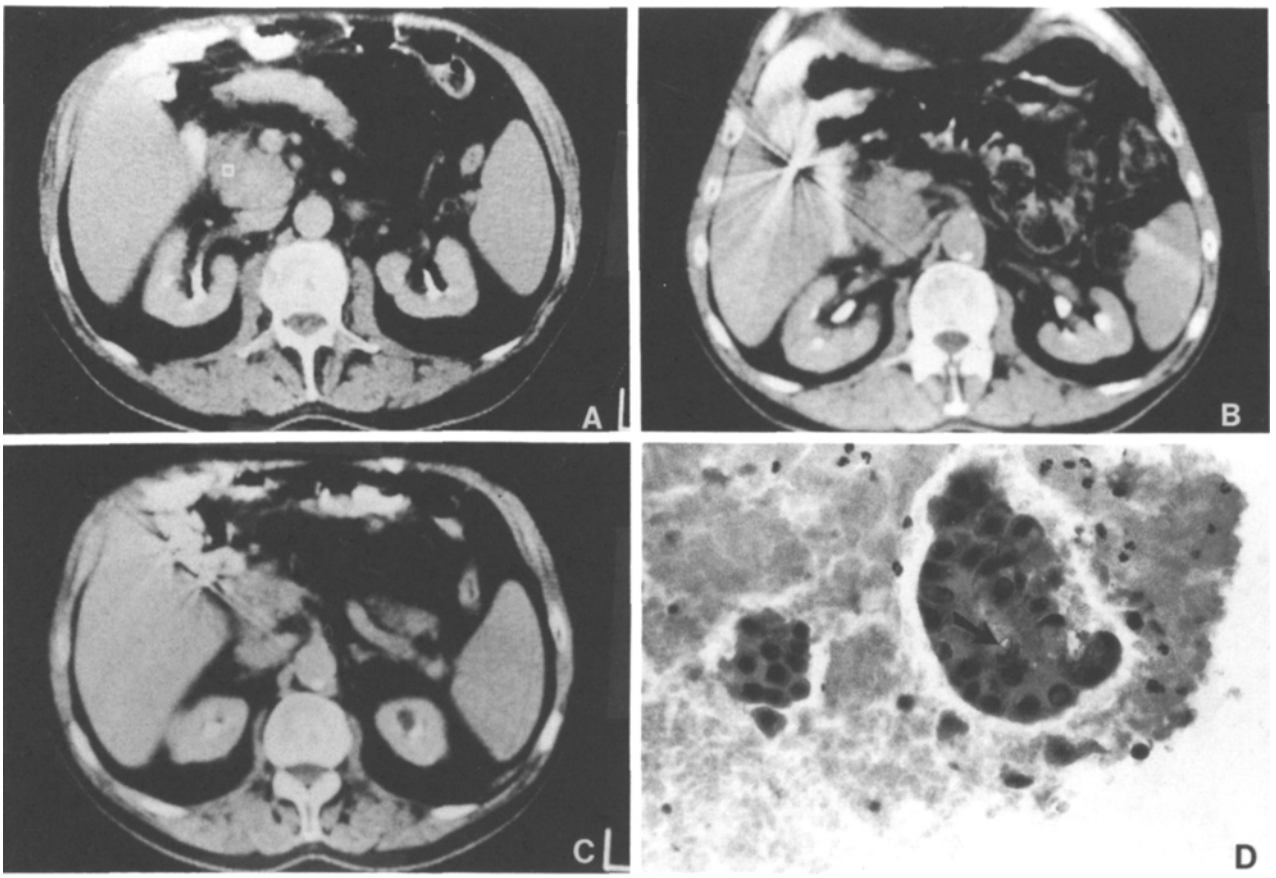

Fig. 4. Case No. 2. A: CT scan in November 1982 showing enlargement of the head of the pancreas consistent with pancreatic adenocarcinoma. B: CT scan in January 1983 showing no clear evidence of change in the size of the tumor in the head of the pancreas. Artifacts from surgical clips in the gallbladder fossa are present. C: CT scan in March 1985 showing persistence of the pancreatic mass. D: Cell block preparation of fine needle aspiration of lesion of rib, showing metastatic adenocarcinoma composed of somewhat pleomorphic cells with moderate cytoplasm. There is evidence of gland formation, and this mucicarmine stain was positive for mucin production in the lumen of this gland (arrow) (×160) Mucicarmine.

Woolf 95% confidence interval of (−2.39,3.33) (Fig. 2, Table 2).

Table 3 compares the above stage D2 prostate cancer patients receiving conventional therapy and on a macrobiotic diet, with literature controls of stage D2 prostate cancer patients receiving conventional therapy and following a standard American diet. Results from study group 3, which utilized questionnaires, are presented in the discussion.

CASE HISTORIES

Pancreatic

Case No. 1. J.K., a 56-year-old man, was diagnosed as having pancreatic cancer by exploratory surgery performed at the University of Indiana Hospital, August 1973. The malignancy was located in the head of the pancreas with metastatic spread to the intestine. He had an incomplete course of chemotherapy postoperatively. One month after discharge, he elected to go on a modified standard macrobiotic diet. Attending physicians re-evaluation of the original biopsy specimen 2 years after initial diagnosis confirmed the original diagnosis of adenocarcinoma.

Seven years after diagnosis, J.K. was hospitalized for fever and abdominal pain. Exploratory laparotomy and biopsies documented the continued presence of adenocarcinoma, grossly and histologically. At surgery, the patient was found to be hemorrhaging from a duodenal ulcer, and he subsequently died in shock and cardiovascular collapse. An autopsy confirmed adenocarcinoma of the head of the pancreas, which had not increased in size, and a large duodenal ulcer. Figure 3 illustrates a section of the duodenal wall showing infiltrative adenocarcinoma. Well differentiated glandular structure can be seen (large arrow). The tumor also shows signet-ring type single cells (small

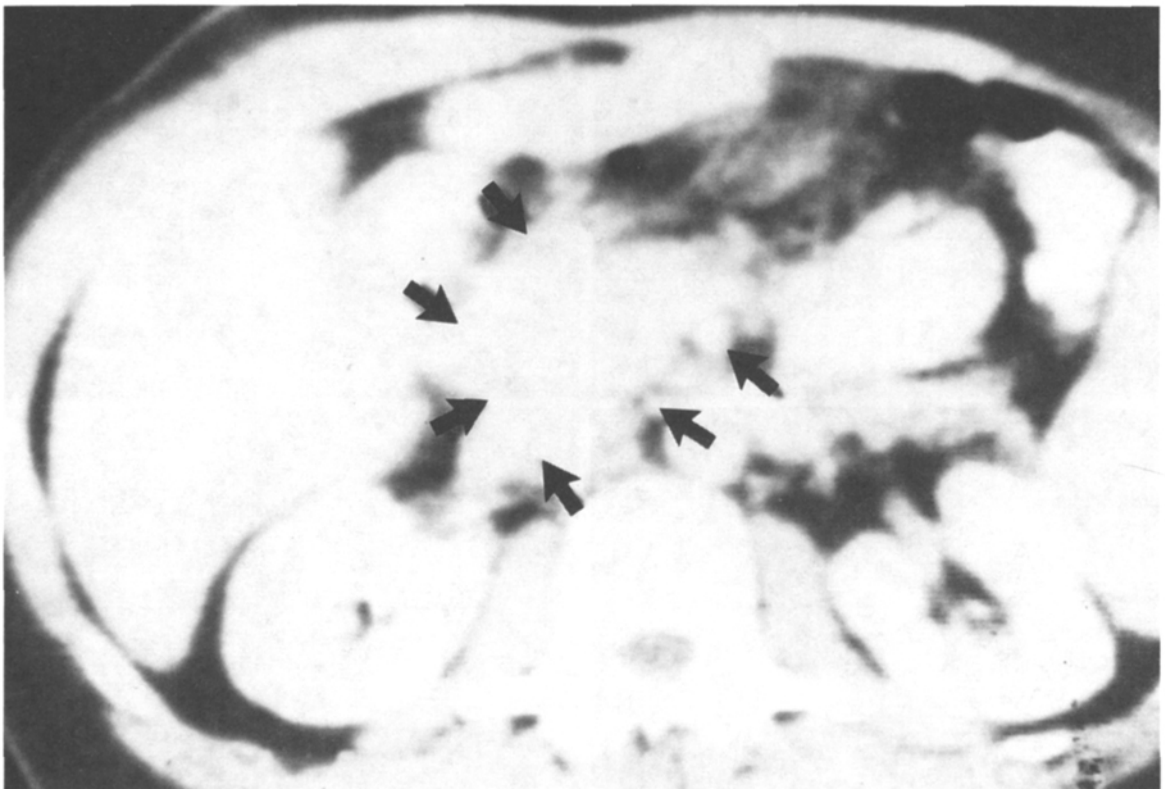

Fig. 5. Case No. 3. CT scan in August 1982 showing enlargement of the head of the pancreas (arrows). These findings are compatible with known pancreatic carcinoma.

arrow).

Case No. 2. C.B., a white male aged 75, was diagnosed with cancer of the head of the pancreas in November 1982 during an exploratory laparotomy. No biopsy was performed, although there was visual inspection of the tumor. Computerized axial tomography (CT) examination performed on admission disclosed enlargement of the head of the pancreas (Fig. 4A). The attending physicians recommended intensive chemotherapy. The patient declined, choosing instead a modified standard macrobiotic diet, that was then instituted. CT scans in January 1983 (Fig. 4B) and March 1985 (Fig. 4C) showed no change in the size of the mass in the head of his pancreas.

After resumption of a standard American diet, with the exception of pork, milk, and eggs late in 1987, a mucin-secreting adenocarcinoma was found in a fractured rib in 1989, at which time he also had a pathological compression fracture of a vertebra and metastatic spread to his liver. C.B. failed to inform the attending physicians of the previous cancer diagnosis of the pancreas as he had considered himself to be cured. Numerous lytic bone lesions, not characteristic of those seen in metastases from adenocarcinoma of the prostate (Fig. 4D), which were considered the primary source, were evident on x-rays. However, adenocarcinoma of the prostate is usually not mucin-secreting. The x-rays and histopathology, therefore, suggest that the C.B.'s primary malignancy was most likely in the pancreas as originally diagnosed. Death resulted 7 years after original diagnosis of cancer of the pancreas in August 1989. An autopsy was not performed.

Case No. 3. Patient N.A., a 62-year-old white male underwent surgery at Providence Hospital, Columbia, SC, on July 28, 1982 for suspected chronic cholecystitis and cholelithiasis. He was found to have an adenocarcinoma of the head of the pancreas with metastases to the iliac nodes and an isolated 1.2 cm metastasis to the liver. Biopsy specimens of the lymph nodes and a wedge biopsy of the liver confirmed metastatic adenocarcinoma of the pancreas. A postoperative abdominal CT scan (Fig. 5) revealed an enlargement in the head of the pancreas with a 2 cm area of decreased attenuation. There was also a 1 cm lesion in the dome of the right lobe of the liver and a 3 mm lesion adjacent to it.

N.A. began a modified standard macrobiotic diet on August 7, 1982. On August 18, 1982, he began a single 5-week course of chemotherapy consisting of 5 treatments with FAM [5-Fluorouracil (5-fu), doxorubicin (Adriamycin), and mitomycin c], at the Lombardi Cancer Center of

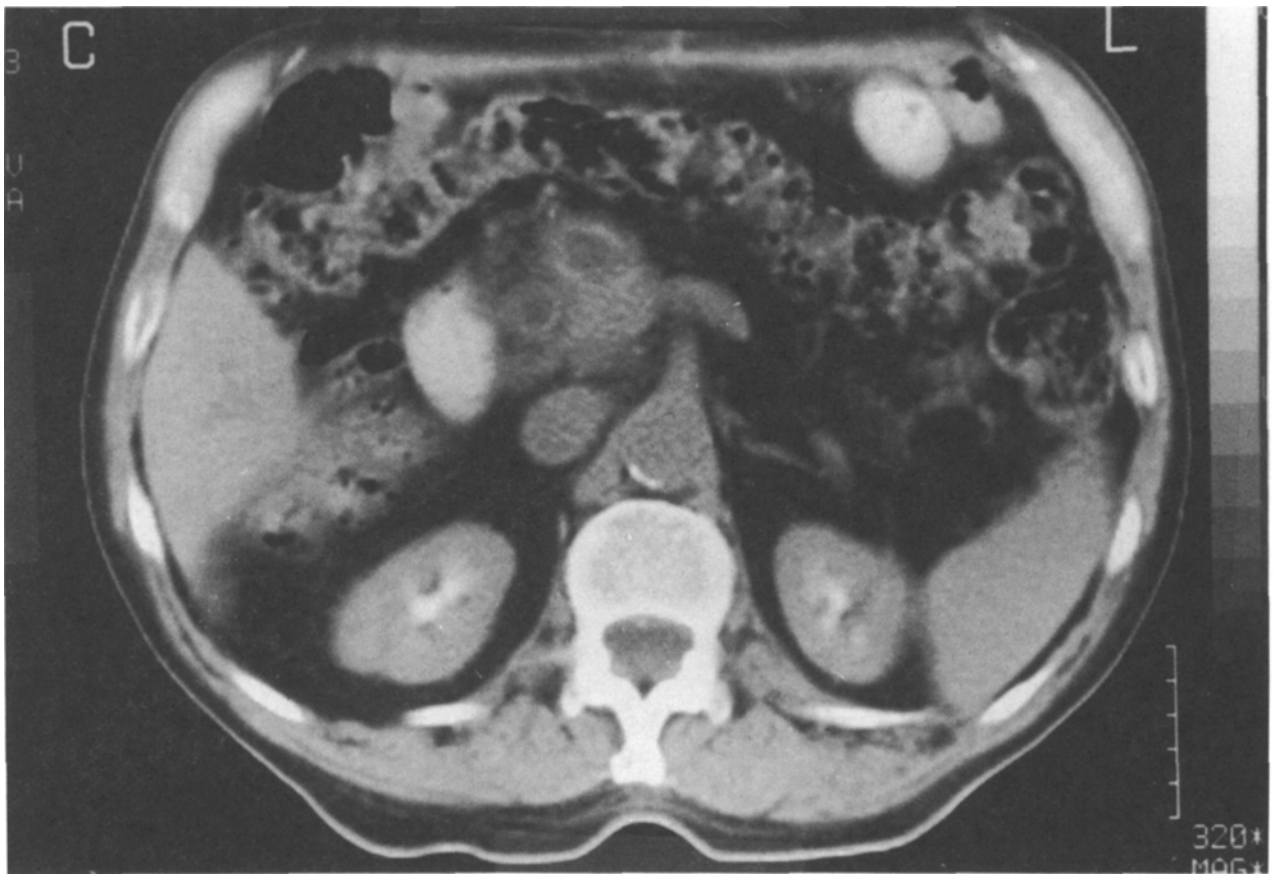

Fig. 6. Case No. 4. CT scan in December 1989 showing pancreatic tumor with cystic necrotic components.

Georgetown University, Washington, DC. On September 23, 1982, he received a single dose of mouse monoclonal antibodies (developed by Dr. Hilary Koprowski of the Wistar Institute of the University of Pennsylvania, and administered by Dr. Henry Sears, of the American Oncologic Hospital in Philadelphia). Physicians at both the Vince Lombardi Cancer Center and the American Oncologic Hospital reviewed the biopsy slides and medical records and concurred in the diagnosis of metastatic adenocarcinoma of the pancreas.

The patient chose to discontinue all forms of chemotherapy after the initial course, but remained on the modified macrobiotic diet. An abdominal CT scan done on December 29, 1982, showed no enlargement of the hepatic metastatic disease of the liver; furthermore, no mass could be defined in the pancreas. In June 1991, nearly 9 years after diagnosis, N.A. remained on the macrobiotic diet and appeared in excellent health.

Case No. 4. H.F., a 76-year-old male underwent an exploratory laparotomy on February 2, 1987. He was diagnosed with adenocarcinoma of approximately 5.5 cm at the head of the pancreas. A gastrojejunostomy, bypassing the partially obstructed area, was performed; tumor biopsy disclosed a poorly differentiated, mucin-secreting adenocarcinoma of the pancreas. No other conventional therapy was prescribed. The patient, however, did go on a modified macrobiotic diet. A CT scan in December 1989 showed the pancreatic tumor to be present and having cystic necrotic components (Fig. 6). Ultrasound a few weeks prior to the CT scan (not shown) also suggested some degree of liquefication of the tumor.

H.F. continues to follow a strict macrobiotic diet with few deviations and, as of April 1992, he remains in good health.

Prostate

Case No. 5. T.S., a 46-year-old man, presented on May 31, 1978, with a tender left chest wall. Physical examination disclosed left rib cage tenderness over the six-seventh rib region, and an enlarged prostate gland. Serum acid phosphatase was markedly elevated. Whole body bone scan (Fig. 7) revealed multiple osteoblastic lesions in the calvarium, right shoulder, thoracic spine, left sixth rib, sternum, and right sacral area. Stage D2 prostate adenocarcinoma was diagnosed and confirmed by a transrectal

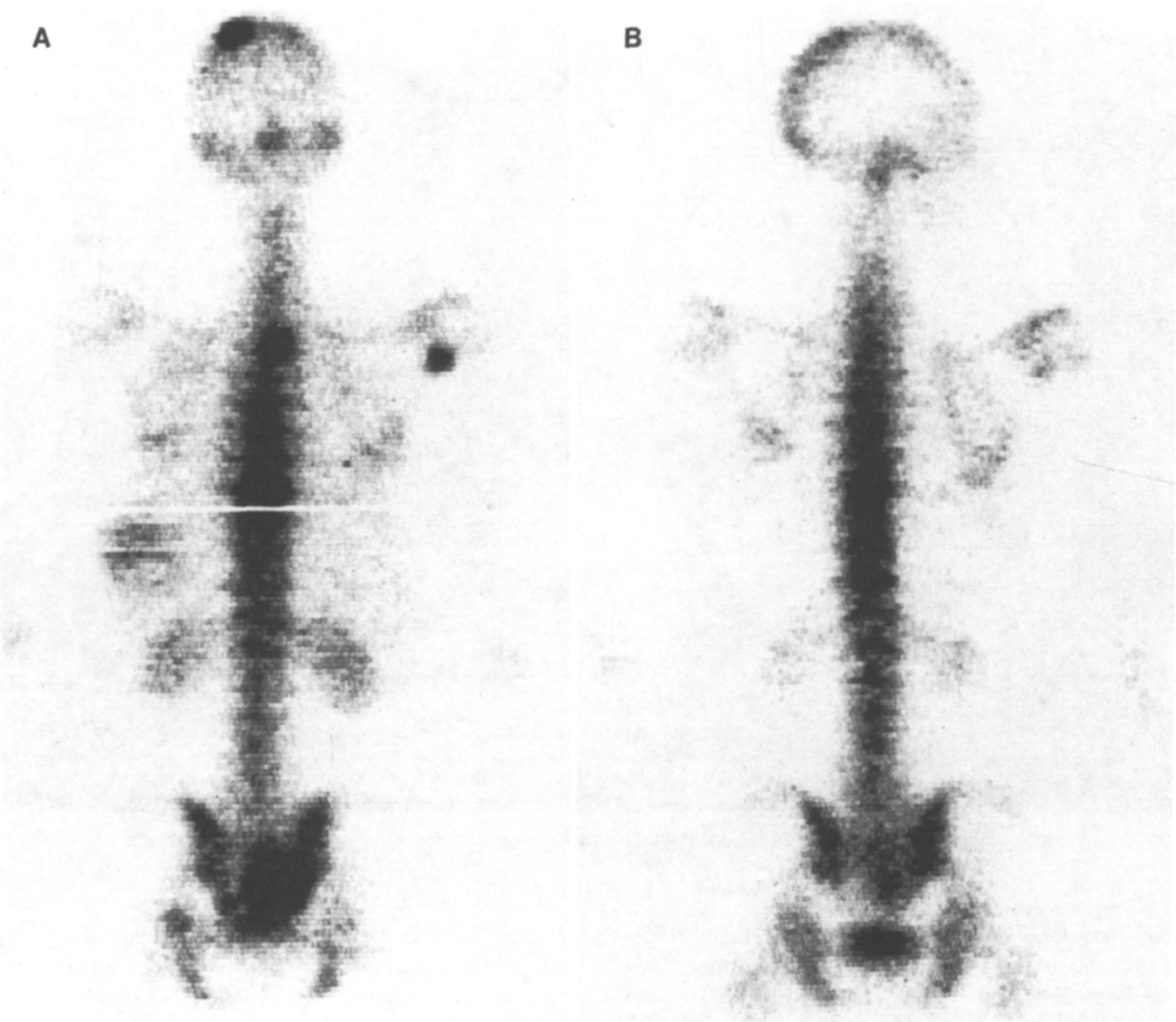

Fig. 7. Case No. 5. A: Whole body bone scan revealing multiple osteoblastic lesions. Stage D2 prostate cancer confirmed by transrectal biopsy of the prostate revealing adenocarcinoma. B: Repeat bone scan, 14 months later, revealing virtually complete resolution of metastatic disease sites.

biopsy of the prostate. The patient underwent a right orchiectomy and right inguinal node dissection. In addition, a portion of the left sixth rib was removed and found to contain evidence of prostate carcinoma. One week later the patient had a left orchiectomy performed. At the time of his initial workup and surgery, survival prognosis was between 18 and 36 months.

The patient was started on a standard therapy regimen which consisted of daily injections of estrogen. With the help of macrobiotic counselors, the patient adopted a strict macrobiotic diet. Fourteen months after diagnosis a repeat bone scan (Fig. 7B) revealed virtually complete resolution of previous focal metastatic disease sites.

For 3 years (1978–1981), T.S. followed the strictest macrobiotic diets prescribed for cancer patients. From 1981–1983, however, T.S. widened his diet to include fish and fruit. In November 1982, a follow-up bone scan (Fig. 8) was negative. From 1984–1987, T.S. further widened the diet to include turkey, tuna fish, and chicken, but no other meats. In December 1987, T.S. had a recurrence of bone pain and bone scintigraphy (not shown) revealed recurrence of metastatic bone lesions throughout the skeleton, T.S. returned to the strictest of macrobiotic diets. No subsequent alteration in disease progress was noted over several months. LHRH analogue and androgen antagonist therapies (Flutamide and Leuprolide) were tried with no success. T.S. died in August 1989, 11 years after his original diagnosis.

Case No. 6. E.H., a 70-year-old male was diagnosed as prostatic carcinoma after biopsy of the prostate revealed a

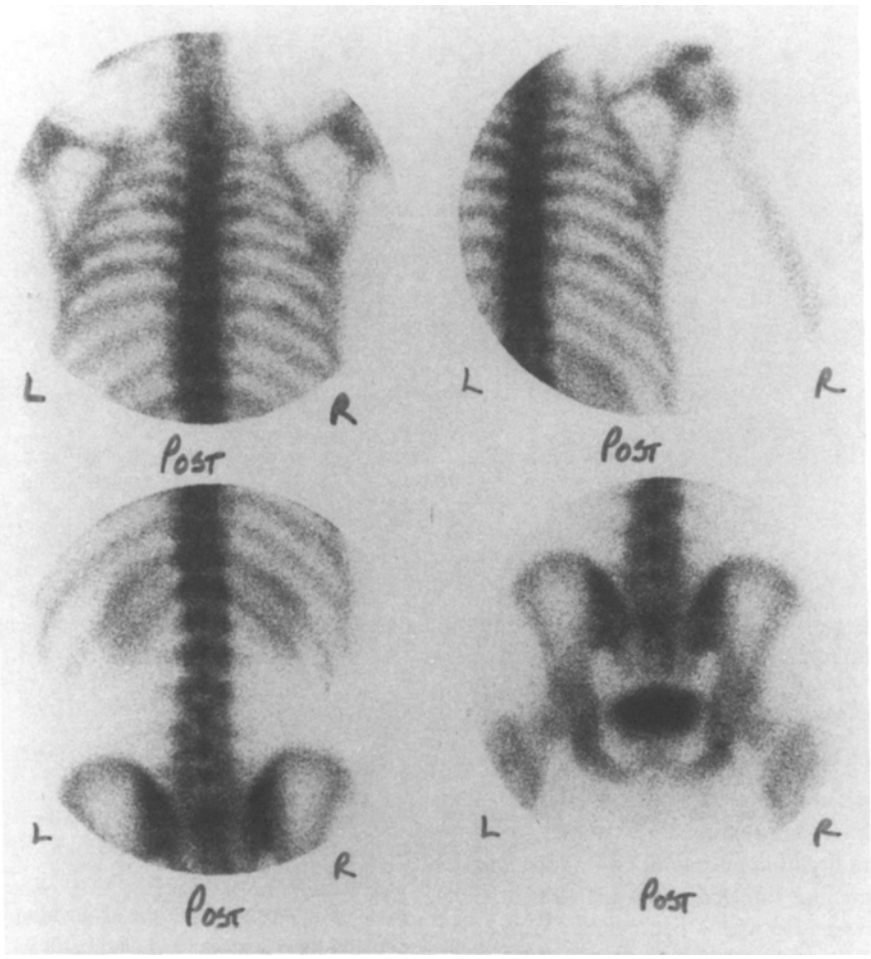

Fig. 8. Case No. 5. Negative bone scan in November 1982.

well differentiated adenocarcinoma (Fig. 9). A bone scan performed early in 1981 (not shown) reportedly showed multiple areas of abnormal radioactivity in the pelvis, ribs, and calvarium. The patient was placed on estrogen therapy for 2½ years. A December 1981 bone scan was negative. Concomitant with initiation of estrogen therapy the patient began a modified macrobiotic diet which was followed strictly until 1984, at which time he widened the diet. Bone scans obtained in 1984 were still negative (Fig. 10). However, recurrence and progression of metastatic bone disease was obvious in December 1986 (Fig. 11).

Case No. 7. C.E.P., a 77-year-old male, presented in late 1981 with a nodular prostate which on biopsy, revealed well differentiated adenocarcinoma of the prostate (Figs. 12A, 12B). Initial bone scintigraphy was negative. The patient had a course of cobalt radiation for 2½ months. In the spring of 1982, he developed increasing pain in the back, shoulders, neck, hips and legs. A bone scan performed in September 1983 (Fig. 13A) showed widespread metastases. He subsequently had bilateral orchiectomy in October 1983. An offer of chemotherapy was declined by the patient. In October 1983, the patient began a strict macrobiotic diet. In May 1984, a repeat bone scan was negative (Fig. 13B) and his acid phosphatase level, previously elevated at the time of the original bone scan, became normal. C.E.P. remained on the strict standard macrobiotic diet for 3 years, then began to follow a more strict version of the diet consisting mainly of grain and vegetables. Annual bone scans have been negative, the most recent study being November 1989. A serum prostate specific antigen in 1991 was negative.

Case No. 8. J.H.D., a 52-year-old male with anemia; weakness; back pain; enlarged, firm, irregular prostate gland; and an elevated acid phosphatase level was hospitalized. Bone scintigraphy revealed multiple bony lesions in the pelvis vertebrae, ribs, calvarium and right femur (Fig. 14). A transrectal biopsy of the prostate gland (Fig. 15A, 15B) showed infiltrating adenocarcinoma of the prostate, Gleason's pattern grade 4–5. The patient had a bilateral orchiectomy and was placed on conventional estrogen

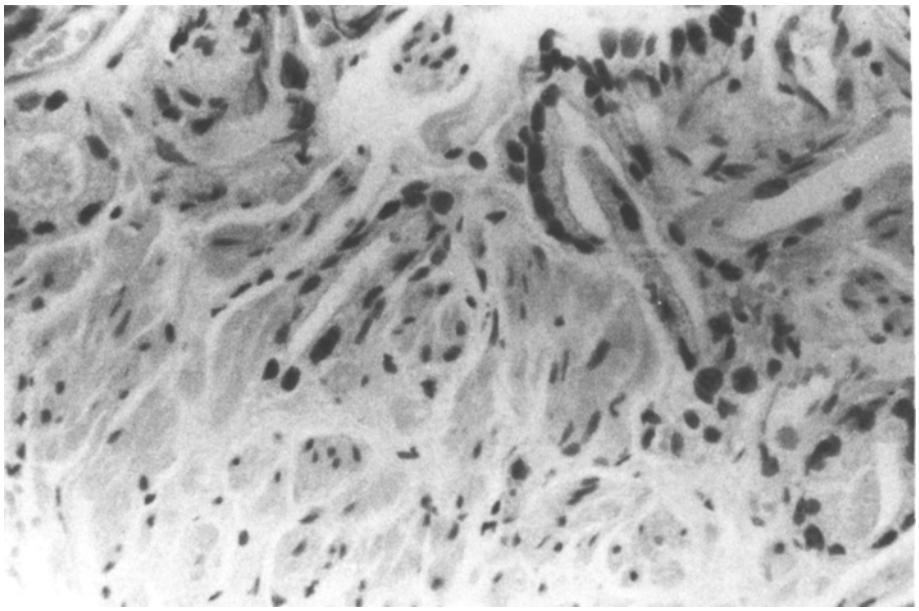

Fig. 9. Case No. 6. Section of prostate needle biopsy showing well-differentiated adenocarcinoma, seen as small glands with single layer of epithelial cells invading stroma (×80).

therapy.

After discharge in July 1984, the patient followed a strict macrobiotic diet for approximately 9 months, after which (April 1985) he began ingesting high-fat foods and alcohol. Upon readmission on December 13, 1985, the patient's hematocrit was 25% with a hemoglobin level of 8 g/dL, and an albumin level of 2.5 g/dL. Despite enteral nutritional support, he continued to deteriorate and died. (While he was in apparent clinical remission, he was consuming 8% of total calories from fat. Relapse occurred when he increased his consumption of fat calories to 17%.)

Case No. 9. C.B., an 88-year-old white male, had been a strict low-fat, high-fiber vegetarian since age 13. In 1970, at age 69, the patient developed prostatism, and a successful transurethral prostatectomy was performed. In 1989, the patient fell, fracturing three ribs and sustaining compression fractures of L2-L4, and required hospitalization. During hospitalization, the patient developed dysuria. Urethrocystoscopic examination revealed residual prostatic tissue which was biopsied and found to be adenocarcinoma with metastatic sites in the thoracic, lumbar spine, and pelvis (Fig. 16). His serum prostate specific antigen was markedly elevated on two occasions.

Orchiectomy was performed December 17, 1989. Immediately following a course of cobalt radiation therapy, the patient's condition deteriorated and he died in January 1990. This case illustrates possible delayed progression of prostate hypertrophy and/or cancer in a life-long, low-fat regimen.

Other

Case No. 10. M.E.G., a 52-year-old female, was admitted to the Emergency Department of Memorial Hospital of Burlington County, NJ, October 27, 1987 with severe pain of 6 weeks duration and vaginal bleeding between periods for 14 months. Diagnostic work-up revealed possible adenocarcinoma. On November 4, 1987, the patient underwent surgery for a total abdominal hysterectomy, bilateral salpingo-oophorectomy, partial omentectomy, appendectomy, and removal of tumor from anterior rectum. The diagnosis of adenocarcinoma (of the endometrium) was confirmed, with either a separate carcinoma of the ovary or with metastases to the ovary, and with metastatic tumor to the serosa of the rectal sigmoid. The disease was stage three, with prognosis of 18 months to 2 years without chemotherapy or radiation, which she refused. She began a macrobiotic diet in January 1988 and remained on a strict diet for one year. Since that time her diet has remained approximately 80% macrobiotic. In February 1991, the patient had a recurrence of vaginal bleeding and adenocarcinoma was found at the apex of the vagina. She underwent her first course of radiation therapy (5000R) to the entire pelvis. No signs of cancer were detected on a follow-up visit in April 1992. Based on the assumption that the patient's illness began in September 1986 with the onset of menstrual bleeding between periods, the patient has survived approximately 6 years to date.

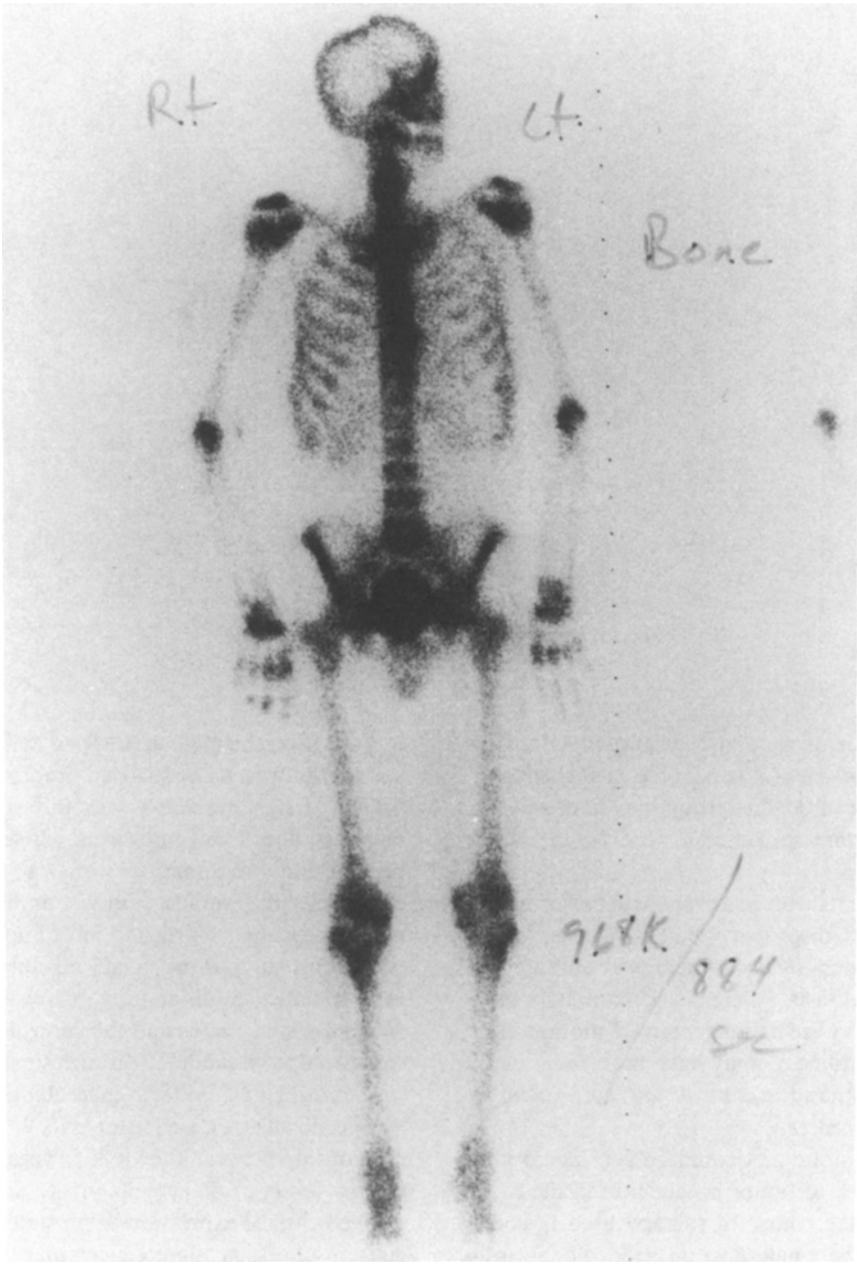

Fig. 10. Case No. 6. Negative bone scan in 1984.

DISCUSSION

While these findings are suggestive of an effect of dietary modification on survival in pancreatic cancer, prostate cancer, and various other cancer cases presented, the small number of cases limits conclusions. The pancreatic study demonstrated a high non-response rate (72/101). It is not known whether or how the respondents might have differed from the non-respondents. There was incomplete medical documentation. (Pathology reports and/or discharge summaries were not received for all of the 28 patients, in which case the patients or next-of-kin had to be relied on to confirm the disease site, stage and histology.)

In addition, while most of the cases (21/23) were reported to have unresectable disease (mainly due to liver metastases) and only one to have tumor confined to the pancreas, we may nonetheless have overstaged them by comparing them with controls with regional or advanced disease. However, pancreatic cancer is far more commonly under-staged than over-staged. Further, the vast majority

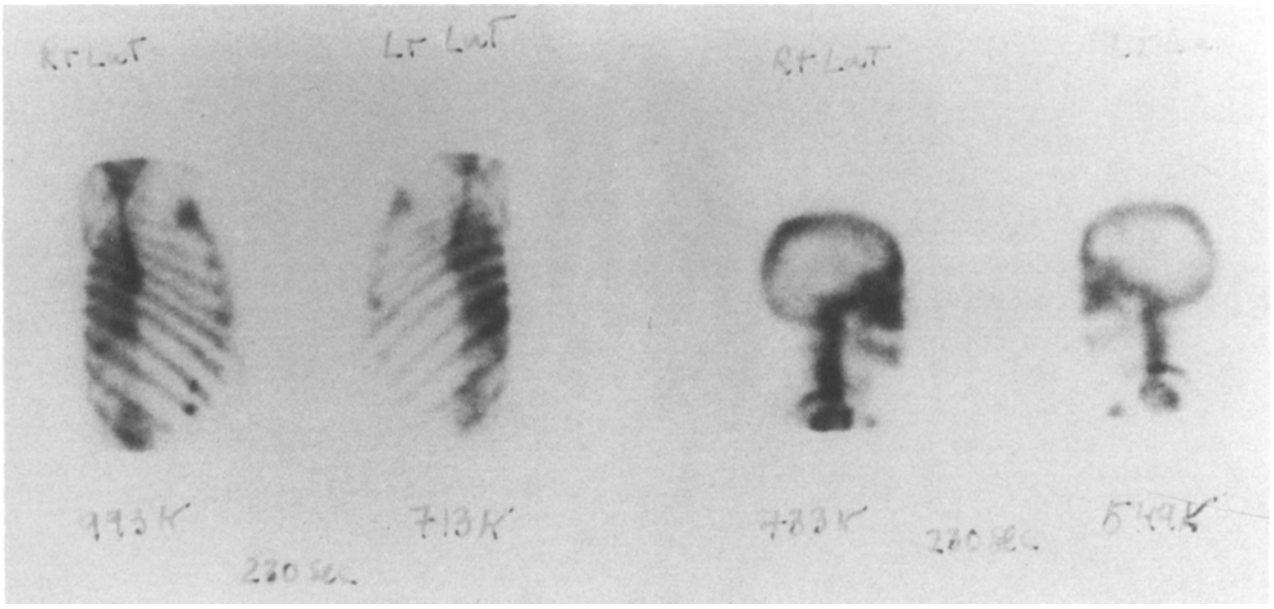

Fig. 11. Case No. 6. Positive bone scan in 1986.

(89.6%) of SEER patients were also diagnosed as having regional or advanced disease. It is possible, that staging or grading biases in favor of the diet group may have existed, i.e., less local and distant spread and more differentiated tumors.

Furthermore, patients with relatively high performance status may have been disproportionately represented in the responding diet group. (Most of them were ambulatory 1–2 months after diagnosis, whereas approximately one-third of SEER controls were no longer alive 2 months after diagnosis.) Innate "hardiness" may have been more characteristic of the cases than the controls and accounted, in part, for survival differences.

Finally, the macrobiotic diet could be considered as a possible reason for lack of tumor progression in the cases briefly presented, as the course of therapy used in some instances, including the single dose of monoclonal antibodies, has not been shown to be effective against pancreas cancer [32]. Thus, it seems plausible that the diet may have not only extended life, but provided quality features not generally seen in pancreas cancer patients (Fig. 1).

In the prostate study, the odds ratio was equal to 1.6, indicating that patients on a modified macrobiotic diet survived longer and were reported to be in better condition than patients who were not. Also, the survival curve (Fig. 2) shows a difference in median survival between cases and controls. Nonetheless, the overall difference in the shape of the curves, sometimes referred to as the rectangularization of the survival curve without overall extension of life, is not statistically significant ($p = 0.20$). However, in this series, the median life span definitely was increased and there was an associated improved quality of life. Several design problems with this study require careful interpretation. First, cases were self-selected, which might bias the study in a manner similar to the "healthy worker effect." Second, subjects did not uniformly follow a strict macrobiotic diet. Third, and most importantly, the sample size of this study is too small, possibly accounting for the lack of statistical differences in overall life extension between the study cases and the controls. Thus, these initial cases need to be extended through single-blind intervention studies utilizing a uniform macrobiotic diet.

Specifically, in Case History No. 9, there is an intriguing relationship between the life-long vegan diet, characterized by low levels of dietary fat intake and the possibility of delayed clinical expression of prostate cancer. Under such circumstances, prostate cancer may have remained dormant for years on a low-fat diet until there was sufficient decline in cellular immunity to allow the cancer to "break through." Research comparing incidence of prostate cancer in Japanese males and Japanese-American males has demonstrated higher rates of prostate cancer among the Japanese-American population attributed to high levels of dietary fat intake [33].

In study group 3, designed to explore the relationship between the modified macrobiotic diet plan and survival length and quality of life characteristics, analysis of the questionnaires revealed: 1) most patients did not stay on a strict macrobiotic diet reliably; 2) most patients went on the macrobiotic diet because they could not tolerate the

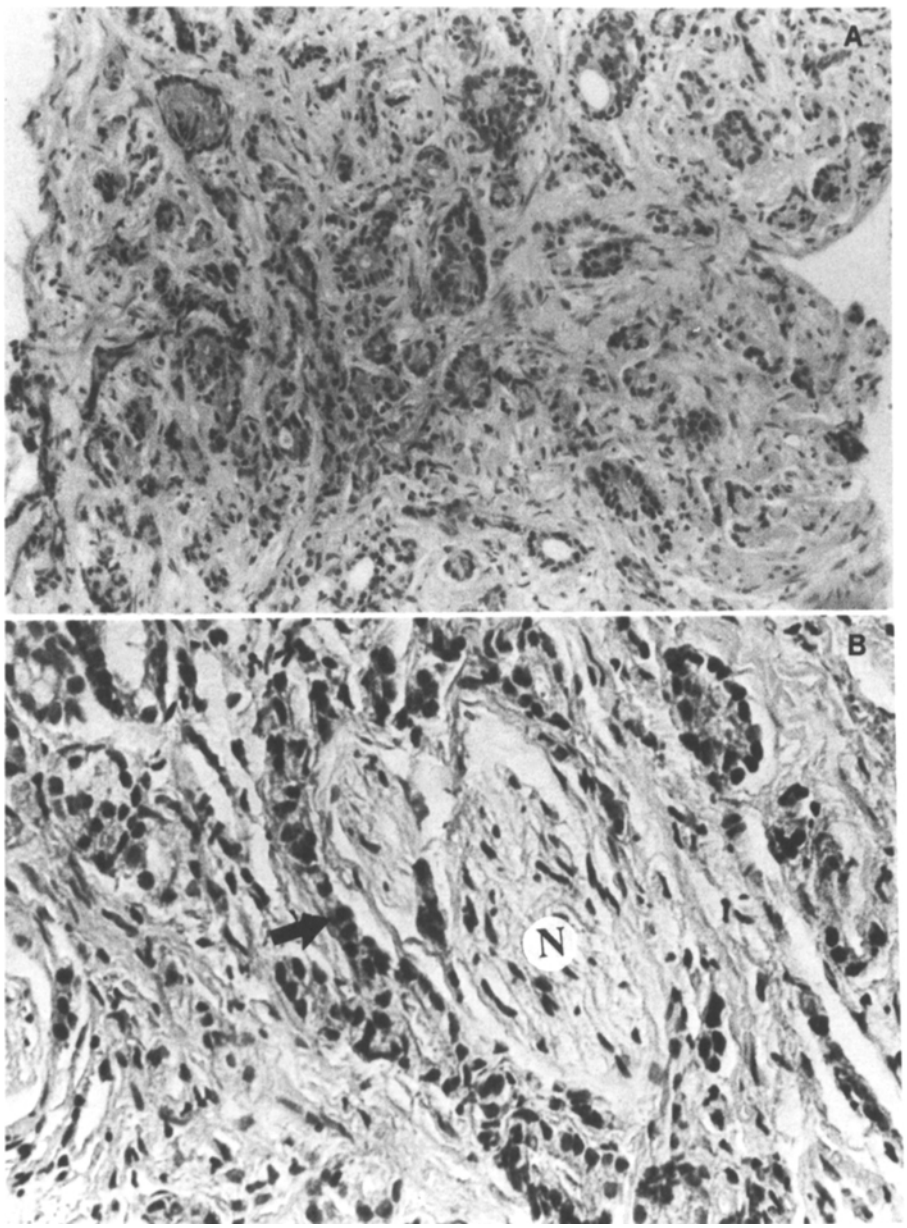

Fig. 12. Case No. 7. A: Section of needle biopsy of prostate showing small, widely spaced neoplastic glands invading prostatic parenchyma (×41). B: Higher magnification of needle biopsy of prostate showing adenocarcinoma with perineureal invasion. Nerve (N) surrounded by neoplastic glands (arrow) (×84).

side effects of chemotherapy and/or radiotherapy, and they wished to try another type of therapy. Analysis of the questionnaires could not distinguish clearly the effects of drug, surgery, radiation and change of diet interventions in patients who had "recovered." However, it is likely that the improved health of those patients whose standard treatment was incomplete, is attributable to the adoption of a macrobiotic diet. Association of renewed progression of the neoplastic process on relaxation of adherence to the diet suggests that a strict macrobiotic diet may be of greatest value.

Similar limitations in the interpretation of results can be observed, which are consistent in all three studies. Subjects may have 1) made only moderate dietary changes rather than adhering to a strict macrobiotic diet, 2) misinterpreted guidelines, and/or 3) lacked outside reinforcement. This may have resulted in an underestimation of the life-extending potential of dietary modification.

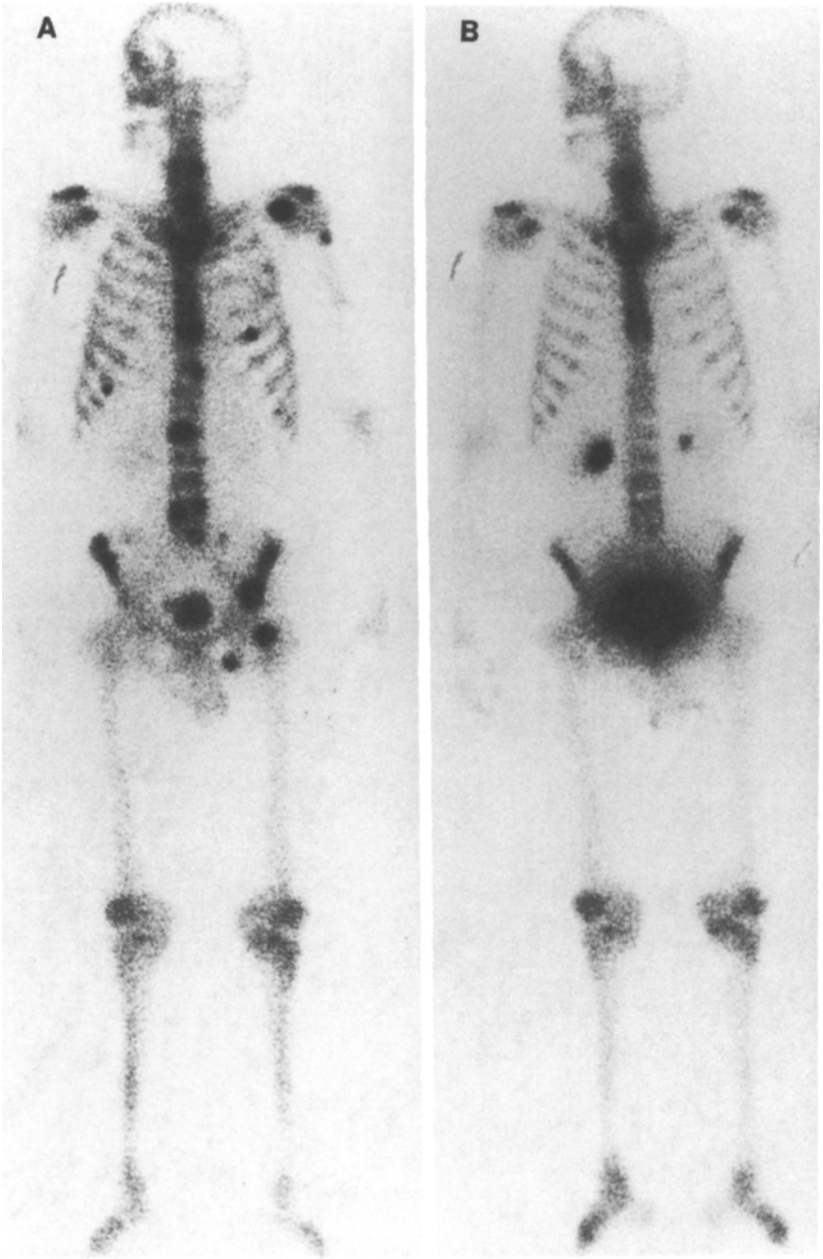

Fig. 13. Case No. 7. A: Positive bone scan showing metastases. B: Negative bone scan.

Patients in the diet group or those reporting dietary modification may have made attitudinal, lifestyle, or other changes that affected their survival. Dietary modification may have constituted only part of a gestalt of healthy, favorable changes made by patients. Yet, the dietary regimen may have had a key role, based on current concepts of mechanisms in nutrition and cancer development.

In both the pancreatic study and the other cancers study, the next-of-kin were relied on to provide retrospective dietary data on behalf of the patients. While this should be regarded as a potential source of bias, a recent study has found that retrospective recall by surrogate for a deceased case can provide reasonably valid dietary intake data, providing that the time since death is not more than several years [11].

This preliminary report lacks details as to micronutrients or fiber constituents that may have been important components of the macrobiotic diet—that provides whole cereal grains and vegetables, as well as being sharply reduced in fat. Whole grains and vegetables are excellent sources of vitamins, and also provide minerals, among which are calcium, potassium, and magnesium, for which

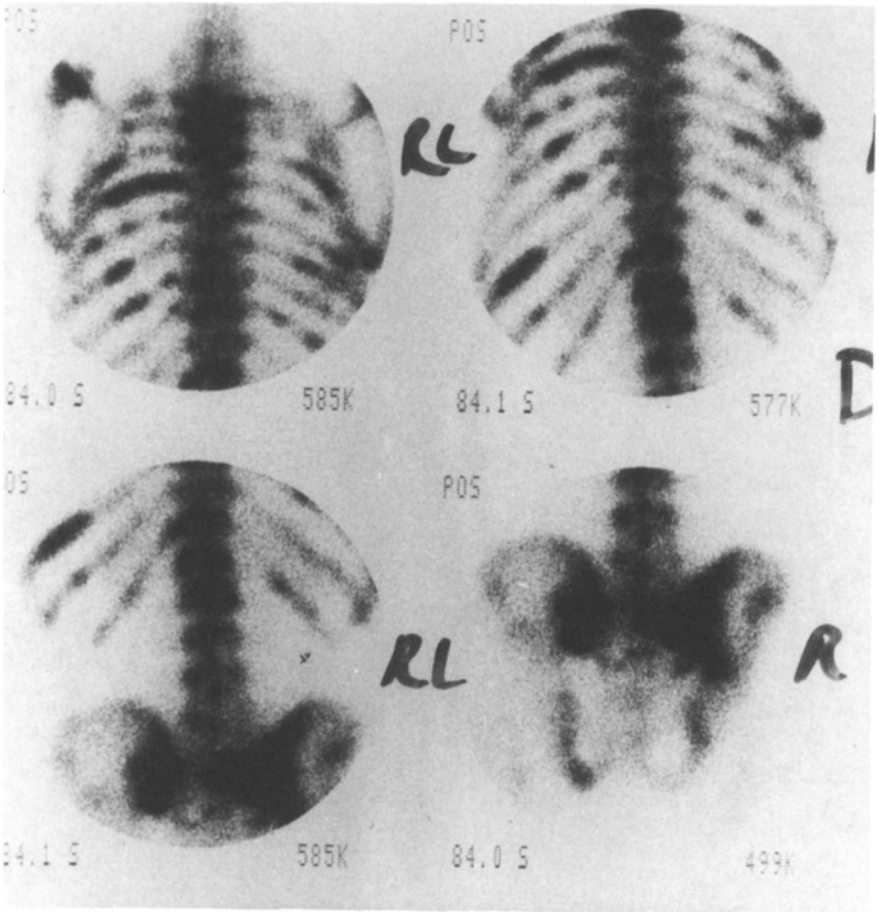

Fig. 14. Case No. 8. Positive bone scan.

there is some evidence suggesting a cancer-inhibiting effect [6]. Magnesium, in particular, has been found to have a protective effect based on its antagonism of calcium [34,35]. On the other hand, calcium ions have a role as second messenger in controlling cell proliferation [35,36].

CONCLUSION

The three sets of studies presented indicate a possible association of dietary modification, involving a high fiber, vegetable and low fat diet, with enhanced survival in primary pancreatic cancer, prostate cancer, and possibly other cancers as well. If this association is indeed causal, it would suggest dietary inhibition of tumor progression in humans, a phenomenon similar to that observed in animal models [37,38]. However, because of the small sample sizes and the possibility of bias in the selection of cases, these findings must be interpreted with caution. Nonetheless, they raise the important question of whether dietary modification may be effective adjunctive treatment to either chemotherapy/radiation therapy and/or surgery, substitution therapy for those refusing standard treatment, or in primary management of cancers whose etiologies have nutritional links, especially when the prognosis with other forms of management is grim. Several cases of apparent remission of pancreatic and other advanced cancers have been documented by pathological findings in patients following this type of dietary modification [39]. There is evidence of recurrence or relapse of cancer after recidivism, "liberalizing," or going off the diet, as well as after stress of major surgery, in several of our patients.

This report is an attempt to examine and piece together evidence that severe dietary modification seems to have extended life and improved its quality in a limited number of cancer patients who had poor prognosis because of refusal to accept full courses of standard antineoplastic therapy. It has the limitations of a retrospective study of patients, not participating in a controlled investigation. Nevertheless, the findings suggest clues that might be investigated in systematic, large-scale clinical trials with matched groups given standard therapy (unless refused) with and without detailed dietary change. Further study is also needed to determine which neoplasms are most likely

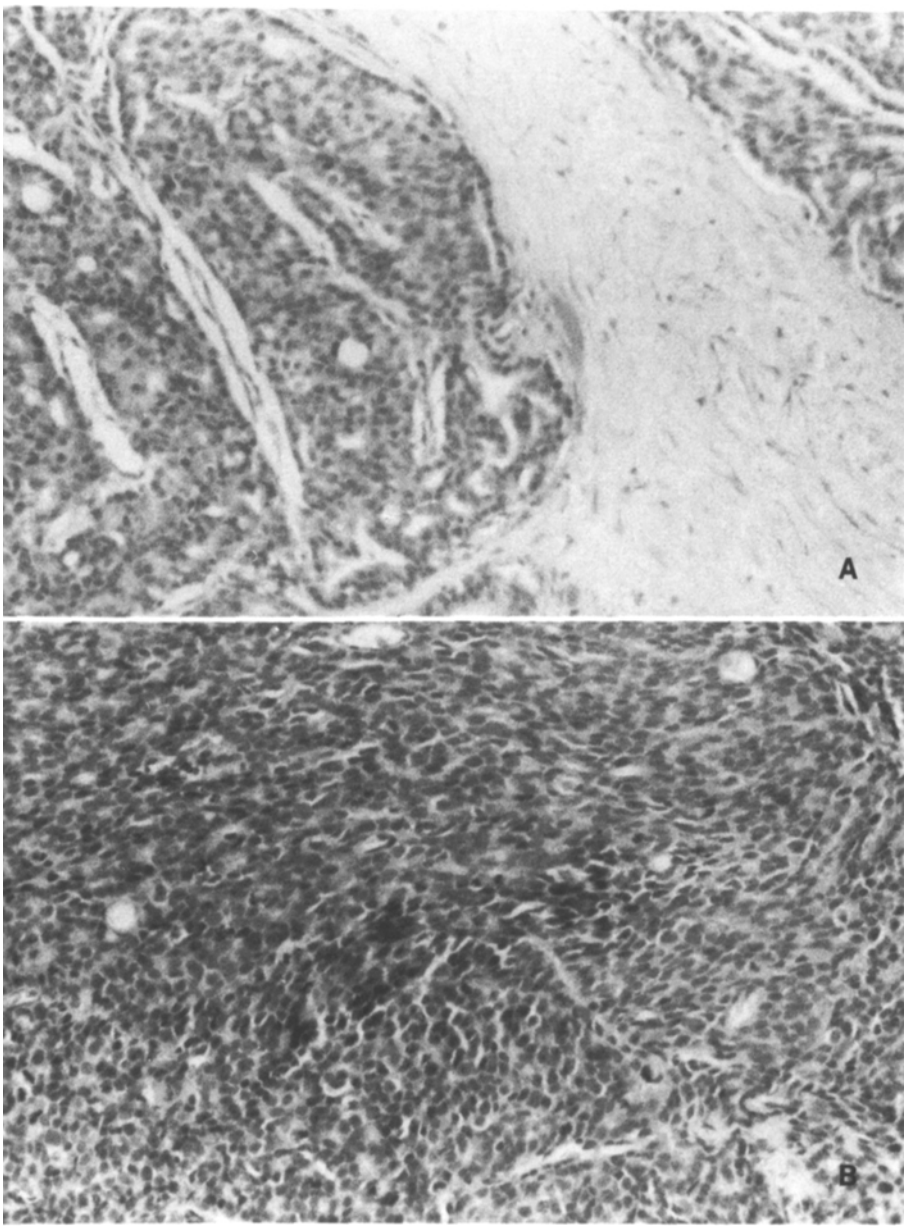

Fig. 15. Case No. 8. A: Section of prostate needle biopsy with infiltrating adenocarcinoma seen as large nests of tumorous glands with "cribriform" pattern of growth (×40). B: Another section of needle biopsy of prostate with tumor forming large, solid, poorly differentiated pattern of growth (×80).

to respond to dietary change. A more general question needing clarification is whether dietary change incorporating some components of the macrobiotic diet can participate in cancer prevention. This exploratory analysis suggests that a strict macrobiotic diet is more likely to be effective in the long-term management of cancer than are diets that provide a variety of other foods. Determining which foods are acceptable additions to the macrobiotic diet would allow for more acceptable dietary changes.

ACKNOWLEDGMENTS

We thank Dr. John Weisburger of the American Health Foundation for his encouragement and support. We also acknowledge the financial support provided by the Kleberg Foundation and the Efamol Research Institute.

Contributions were also made by Nila Garces, PhD, for epidemiologic guidance in designing and carrying out the pancreatic cancer study and Janet Rice, PhD, Syed Islam,

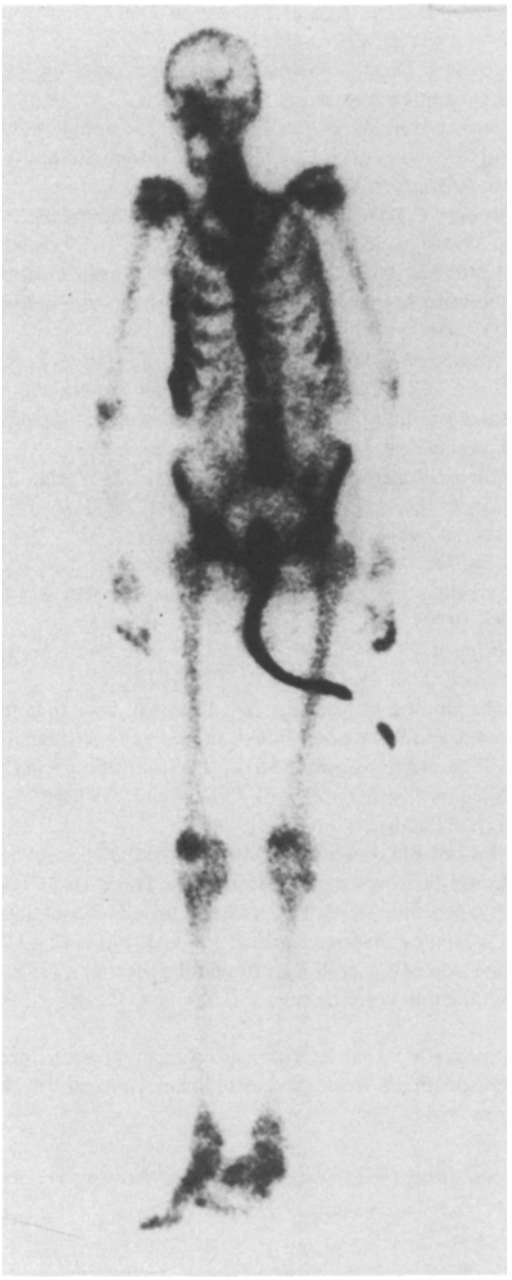

Fig. 16. Case No. 9. Anterior whole body bone scan. Multiple lesions are evident in the rib cage, left ilium, left paroximal femur and lumbar spine.

MPH, and Lawrence Kushi, ScD, who provided biostatistical and epidemiologic consultation. The following graduate and undergraduate students helped in review of the literature and preparation of the manuscript: Maria Ludwick, MPH; Linda Fanning, RD; Mary Schmidt; Jodi Schaeffer; Willa Hatter; Earnest Charles; Alicia Hillman; Heidi Hampton, RD; Rana Bayakly, MPH; and Pierre Ngoumou, MD, PhD.

This paper is dedicated to the memory of Dr. James Welch, a cardiovascular surgeon who adopted a low-fat, high-fiber diet as adjunctive treatment for colon cancer, and was convinced of its benefit.

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Received June 1992; revision accepted November 1992.