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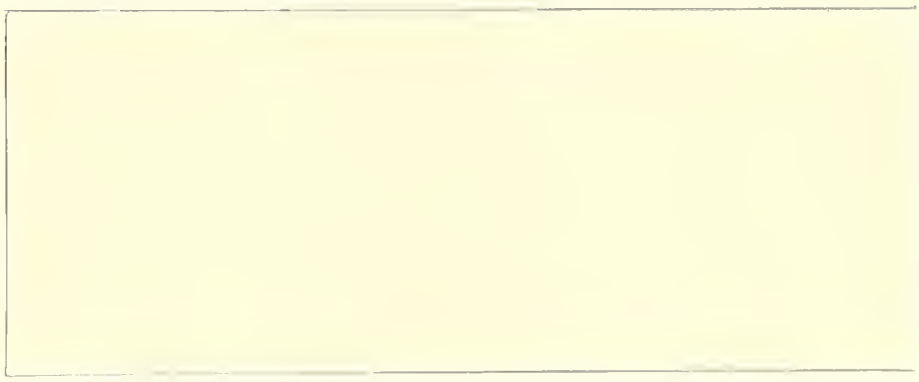

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SOCIAL AND ECONOMIC CAUSES OF CANCER*

by

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1. Introduction

People of lower socioeconomic status are more likely to contract and die from cancer. This finding has been consistently observed no matter how "socioeconomic status" is defined-- by income, educational attainment, occupation, housing tenure, census tract of residence, race, ethnicity, or by public versus private hospital care.[1]

In this essay I ask: How could an individual's socioeconomic status be a "cause" of his or her cancer? To answer such a question, I shall view the development of cancer as a protracted process that takes place in multiple stages in an individual over many years. The rates of transition between stages, I shall suggest, may be affected not only by conventional "carcinogens" such as chemicals, viruses and radiation, but also by social and economic conditions.

In essence, my idea is to expand the narrow definition of "carcinogen" beyond those identifiable physicochemical agents that we usually regard as "causing" cancer. In doing so, I do not intend to downplay the role of the established carcinogens. In fact, I shall suggest that social and economic conditions may interact synergistically with such identifiable agents.

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[1]. See American Cancer Society 1986; Axtell, Asire and Myers 1976; Berg, Ross and Latourette 1977; Brown, Selvin and Winkelstein 1975; Buell, Dunn and Breslow 1960; Clemmesen and Nielsen 1951; Cohart 1954, 1955ab; Dayal et al 1984; Devesa and Diamond 1983; Dorn 1944; Dorn and Cutler 1959; Graham, Levine and Lilienfeld 1961; Haan and Kaplan 1985; Hakama et al. 1982; Henschke et al. 1973; Jenkins 1983; Kitagawa and Hauser 1973; Knight and Dublin 1917; Kogevinas 1987; Lombard and Doering 1929; Marmot and McDowell 1986; Marmot, Kogevinas and Elston 1987; Salonen 1982; Seidman 1970; Williams and Horm 1977; Yeracaris and Kim 1978.

Among the individual, identifiable agents are the so-called "occupational" carcinogens. These agents-- such as chromium, dischloromethyl ether, nickel, vinyl chloride, and radon daughters-- have been termed "occupational" carcinogens because people are exposed to them primarily as workers on the job. Many of these jobs-- copper smelters, shipyard workers, roofers, asphalters, miners, and leather workers-- might be filled by workers from the lower socioeconomic strata; but this is not what I mean by a socioeconomic "cause" of cancer. Instead, my focus is on occupational and other social-economic conditions for which specific agents have not been identified. For example, I shall be concerned about the possible relation between cancer, immune defenses, and unemployment (Arnetz et al. 1987) which, after all, is also an occupational category.

Likewise, persons of lower socioeconomic status may reside in places that are more exposed to pollution through the air, water, and other media. I do not analyze whether exposure to specific chemicals, such as polyaromatic hydrocarbons in air or polychlorinated biphenyls (PCBs) in water, are higher in poor neighborhoods.

Among the most important identifiable carcinogens is cigarette smoke, which causes specific cancers among persons in all socioeconomic groups. I do not determine what proportions of such cancers among persons of lower socioeconomic status might be attributed to their cigarette smoking, either alone or in combination with other exposures, such as asbestos in the workplace or alcoholic beverages. For smoking-sensitive neoplasms, such as cancers of the lung and esophagus, attempts to identify an independent contribution of socioeconomic status have yielded ambiguous findings at best

(Brown, Selvin and Winkelstein 1975; Devesa and Diamond 1983; Fox and Adelstein 1978; Pottern et al. 1981; Williams and Horm 1977). Socioeconomic gradients in incidence and survival have been observed, however, for cancers that are not known to be sensitive to cigarette use.

Instead, I focus specifically on interactions between cigarette smoking and the less well-delineated features of lower socioeconomic status. One notable example is the potential interaction between cigarette smoking and certain viral infections in the genesis of cancers of the uterine cervix (Brinton et al. 1986; Holly et al. 1986; Winkelstein et al. 1984), liver (Austin et al. 1986; Trichopoulos et al. 1987), and oral cavity (Schantz et al. 1986; Shillitoe et al. 1982). More careful attention, I shall suggest, needs to be given to the relations between socioeconomic characteristics and certain viral infections, as well as the potential interactions between such viral infections and specific agents in the development of cancer (Rous and Kidd 1936, 1938; Schrier et al. 1983; Winkelstein et al. 1984).

Black persons in the United States have higher incidence and mortality rates from many cancers (Henschke et al. 1973); they also are more likely to be economically disadvantaged. Although much of the excess of cancer among black persons may be a consequence of their lower socioeconomic position, I do not resolve whether any of the excess is somehow intrinsic to being black (American Cancer Society 1986; Berg, Ross and Latourette 1977; Devesa and Diamond 1983; Lerner 1986). Being black is clearly protective for certain skin cancers. A number of known genetic conditions that predispose to cancer occur predominantly among white persons (Swift et al. 1987; Schimke 1978). What matters in this essay is the acquired, not the inherited.

Finally, morbidity and mortality from cancer can surely impair productivity, cut short education, divert family resources, and reduce wealth. I acknowledge such issues of reverse causality,[2] and discuss them no further.

In Sections 2, 3 and 4, respectively, I analyze social and economic influences on three specific cancers-- the breast and uterine cervix in women, and melanoma of the skin in whites. These cancers display very different, contrasting relationships to socioeconomic status. For breast and cervical cancer, moreover, there is little current evidence to incriminate occupational carcinogens. For melanoma, white-collar workers appear to have the highest incidence; moreover, with one exception (Bahn et al. 1976), I know of no identifiable carcinogenic agents associated with the disease.

Having considered some illustrative cases in detail, I turn in Section 5 to cancer in general. In particular, I examine current knowledge of human cancer as a multistep process, and begin to identify how social and economic conditions might impinge upon each step.

The remaining sections analyze two specific mechanisms in detail. Section 6 considers the potential effects of social and economic stresses on the body's immune defenses to tumor development. Section 7 investigates the role of social and economic factors in the timing and content of medical care for cancer. An agenda for future research is outlined in Section 8.

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[2]. See Bartel and Taubman 1979; Duleep 1985; Farrell and Fuchs 1982; Fox, Goldblatt and Jones 1985; Luft 1975, 1978; Parsons 1977; Reynolds 1980; Wilkinson 1986.

2. Breast Cancer: Early Detection and Reproductive History

I begin with breast cancer-- a specific and important exception to the general rule that people of higher socioeconomic status have less cancer. In fact, women in the upper socioeconomic strata have a higher incidence of breast cancer than women in lower socioeconomic groups (Cohart 1955a; Dorn and Cutler 1959; Hakama et al. 1982; Hirayama, Waterhouse and Fraumeni 1980; Kitagawa and Hauser 1973; Williams and Horm 1977).

While upper class women may contract more breast cancer than lower class women, this does not mean that upper and lower class women get the same kinds of breast cancers. For example, at the time of diagnosis, upper socioeconomic women tend to show a higher proportion of localized breast cancers that have not metastasized to the lymph nodes or to other body organs.[3] It is not obvious, however, whether such localized cancers can alone account for the higher incidence among upper class women.[4] Nor is it clear whether socioeconomic differentials in incidence or staging of breast cancer have changed since the advent of mammography in 1956[5] or since the enactment of Medicare and Medicaid legislation in the United States in 1966.[6]

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[3]. See Axtell, Asire and Myers 1976; Axtell and Myers 1978; Berg, Ross and Latourette 1977; Dayal, Power and Chiu 1982; Linden 1969; Lipworth, Abelin and Connelly 1970.

[4]. The most reliable data are on black-white differences. Based upon results from the 1969-71 Third National Cancer Survey (Cutler and Young 1975) and the Cancer Surveillance, Epidemiology and End Results (SEER) Program (Axtell, Asire and Myers 1975), I compute that white women have annual incidence rates of 36 localized cancers and 39 nonlocalized cancers per 100,000 persons. The corresponding black incidence rates are 19 localized cancers and 39 nonlocalized cancers per 100,000. While these data suggest that all of the black-white incidence differential reflects localized disease, they may not accurately reflect differences due to socioeconomic status.

[5]. See Egan 1962; Habbema et al. 1986; Shapiro 1977.

[6]. According to the SEER data, among newly diagnosed white cases, the proportion of localized tumors increased from 41% in 1950-54 to 48% in 1970-73. Among newly diagnosed black cases, the corresponding proportions were 29% in 1950-54 and 33% in 1970-73. Whether the SEER data accurately reflect the incidence or case-mix of breast cancers, however, remains unclear (Doll and Peto 1981).

Cancer Survival. Once their breast cancers are identified, however, women of higher socioeconomic status have longer disease-free intervals and more favorable survival. The improved survival is not solely the result of more localized tumors in upper class women. It is observed even when the comparison is restricted to cases of the same clinical staging, or to cases of the same age.[7] There are likewise insufficient data to ascertain whether socioeconomic differences in survival have changed since the advent of adjuvant chemotherapy in the mid-1970s (Ries, Pollack and Young 1983). The most reliable evidence comes from death rates, which show the combined effect of changes in both incidence and survival. The overall age-adjusted death rate from breast cancer among white women was 22.4 per 100,000 in 1960, 23.4 per 100,000 in 1970, and 22.8 per 100,00 in 1980; among black women, the corresponding death rates were 21.3, 21.5, and 23.3 per 100,000 (U.S. Department of Health and Human Services 1985). These black-white differentials, however, are poor proxies for socioeconomic differences.

Why the Higher Incidence Rates in Upper Socioeconomic Women? One is tempted to explain the gradients in incidence and survival as entirely the consequence of improved cancer detection and better treatment. Thus, women in the upper social and economic strata are more likely to identify and seek care for early symptoms of cancer. Having identified such symptoms, they have better access to diagnostic and therapeutic medical services. Having obtained

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7. See Axtell, Asire and Myers 1975; Axtell and Myers 1978; Berg, Ross and Latourette 1977; Cohart 1955a; Dayal et al. 1982; Linden 1969; Lewison, Montague and Kuller 1966; Lipworth, Abelin and Connelly 1970; Ries, Pollack and Young 1983 Young, Ries and Pollack 1984. From the 1960-73 SEER data (Axtill, Asire and Myers 1975; Axtell and Myers 1978), I compute that the higher proportion of clinically localized tumors account for only about half of the survival advantage of white over black patients.

such services, they are better equipped to adhere to medical instructions. Having received care, their overall standard of living makes treatment more effective.

As I discuss in Section 7, there is reasonably good empirical support for most of these assertions. But they may not tell the whole story.

The observation that breast cancer patients in the higher socioeconomic groups have more localized tumors and better survival rates is applicable to many other malignancies.[8] But the higher incidence of breast tumors in upper class women needs explaining. To make a cogent case for improved detection as the sole explanation for the higher incidence, we would need to postulate that the additional cancer cases detected in such women are in fact much less virulent forms of the disease. In that case, the incidence data would overstate the excess of genuinely malignant cancer among upper class women. Instead, through self-examination, doctor check-ups and mammography, gross and microscopic lesions are discovered that would otherwise remain quiescent and thus go unidentified during life. But is there any biological basis for such a speculation?

The Receptor Story. It has been suggested that many breast lesions which are histologically cancerous to the pathologist under the microscope are actually clinically benign (Fox 1979). Indeed, there is increasing evidence that histologically similar breast tumors may be highly heterogeneous. One important source of heterogeneity is the presence or absence of "hormone

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[8]. See Axtell and Myers 1978; Berg, Ross and Latourette 1977; Cohart 1955ab; Dayal and Chiu 1982; Dayal, Power and Chiu 1982; Linden 1969; Lipworth, Abelin and Connelly 1970; Nomura et al. 1981; Pendergrass, Hooever and Godwin 1975; Ries, Pollack and Young 1983; Wegner et al. 1982; Young, Ries and Pollack 1984.

receptors" on breast cancer cells. These receptors are only identifiable by means other than the pathologist's microscope. The presence in the cancer specimen of one particular receptor, called a "cytosolic estrogen receptor," appears to predict a lower level of malignancy, as well as a favorable response to certain types of therapy.[9]

Among post-menopausal breast cancer cases (and probably pre-menopausal cases), a higher proportion of white women's tumors in fact display such cytoplasmic estrogen receptors (Beverly et al. 1987; Mohla et al. 1982; Pegoraro et al. 1986). While the higher proportion is arguably the result of genetic differences between races, environmental factors could be important. No study of estrogen receptors among breast cancer patients has focused specifically on measures of socioeconomic status. But if environmental conditions do affect the presence or absence of estrogen receptors, the question is how?

Pregnancy History and Cancer. Women of lower socioeconomic position become pregnant for the first time at earlier ages than do women in higher strata. Epidemiologic analyses indicate that a lower age at first full term birth protects against subsequent breast cancer (MacMahon et al. 1970). The effect is quantitatively significant. Women who have their first full term pregnancy before the age of 22 have about one-third the risk for breast cancer of those whose first pregnancy is after age 30.

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9. Whether the presence or absence of such estrogen receptors is a consistent feature of a particular tumor over its lifetime is still unknown. The fact that there are fewer such receptors in samples taken from metastatic sites of breast cancers suggests tumors may lose their estrogen receptors as they become more malignant (Mohla et al. 1982).

Early first pregancy appears to reduce the number of estrogen receptors in normal breast tissue. In a recent study, breast cancer patients whose tumors were rich in estrogen receptors were found more likely to have late first pregnancies (McTiernan et al. 1986). Early first pregnancy among women of lower socioeconomic status thus appears to eliminate those mammary cells that might ultimately yield less malignant forms of disease. If so, then differences in pregnancy history among women of varying social background could explain their observed differences in cancer incidence and survival.[10]

Early and Late Influences on Cancer. We thus have two explanations for the observed differences in breast cancer incidence and survival among women of different social status: reproductive history, especially the timing of the first full pregnancy; and access to cancer detection and treatment. These two explanations reflect events at quite distant points in the life cycle. Menarche and first pregnancy are early life events. They precede by many

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10. There may be other mechanisms whereby early first full term pregnancy reduces breast cancer risk. A woman's first delivery appears to produce a long-term reduction in the secretion of the pituitary hormone prolactin (Kwa et al. 1981; Musey et al. 1987). In animal experiments to be described in Section 5, prolactin promotes the growth of breast cancers that have been initiated by other agents (Manni, Trujillo, and Pearson 1977; Pitot 1982). Elevated prolactin levels predict subsequent breast cancer in post-menopausal women (Kwa et al. 1981).
The timing of the first delivery is not the only relevant feature of reproductive history. Early onset of menstruation and later onset of menopause, which are both more prevalent in women of higher socioeconomic position, are also predictive of higher breast cancer risk. Estrogens and prolactin both increase the mitotic activity of breast epithelium. Such mitotic activity is particularly enhanced during normal menstrual cycles, whereas it is reduced after menopause. Early menarche and late menopause may therefore promote the development of breast cancer by increasing the number of normal menstrual cycles and thus the total lifetime exposure of breast tissue to estrogens and prolactin. Given that there is a permanent reduction of prolactin following the first pregnancy, the number of normal menstrual cycles prior to the first pregnancy may be especially critical in the development of mammary cancers (Pike et al. 1983).

years the development of a clinical breast cancer in an afflicted person. Detection and cancer care are, in comparative terms, later life events.

This critical distinction-- between factors that influence the early genesis of cancer and those that affect its later progression and morbidity-- is of considerable importance and will be discussed in more detail in Section 5. Later-stage influences on cancer should reflect contemporary and more recent social and economic conditions, whereas early-stage influences should reflect socioeconomic conditions prevalent in the more distant past. The median age of breast cancer diagnosis is about 57 years (Axtell, Asire and Myers 1975), so that the median year of birth of women now incurring breast cancer is about 1930, and the median year of menarche is about 1943. For this cohort, socioeconomic differences in the timing of first birth during 1945-1965 could be critical.

Many economists have described how education, one indicator of socioeconomic position, may permit an individual to "produce" his or her own health more "efficiently" (Grossman 1975). Others have noted that to some degree, education and health are "produced jointly" (Farrell and Fuchs 1982). The fact that more educated women are more likely to identify and seek treatment of early breast lesions may be an example of the former phenomenon. The fact that women with less education start families at earlier ages may illustrate the latter. The economic distinction between education as an input to health and education as produced jointly with health corresponds, in a rough way, to the biological distinction between late-stage and early-stage facilitators of carcinogenesis.[11]

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11. While I concentrate on reproductive history and access to care, nutrition also needs to be considered. Various aspects of nutrition-- fat, fiber and caloric intake, the consumption of such specific constituents such as minerals and fish oils, and total body weight-- have been repeatedly cited as influencing cancer in general and breast cancer in particular (Benson, Lev and Grand 1956; Bonser and Wainman 1940; Carroll et al 1986; Dunning, Curtis and

3. Cervical Cancer: Pap smears, Promiscuity, and Cigarettes

In contrast to breast cancer, the incidence of invasive cancer of the uterine cervix is elevated among women of lower socioeconomic status (Clemmesen and Nielsen 1951; Cohart 1955a; Hakama et al. 1982; Williams and Horm 1977). Like breast cancer, however, newly diagnosed cervical cancers in women of lower social status less likely to be localized. Moreover, they carry a poorer prognosis (Axtell, Asire and Myers 1975; Lipworth et al. 1970). While breast cancers vary considerably in their histopathology, over 85 percent of invasive cervical cancers are of the squamous cell type. The overall incidence and mortality from cervical cancer have been declining in the United States since at least 1950. The death rate from cervical cancer has been declining notably faster in whites than in blacks.

The influence of socioeconomic status on morbidity and mortality from cervical cancer may entail three different mechanisms: the use of pap smears; individual sexual practices; and cigarette smoking.

Pap Smears. Regular pap smears can detect early cervical cancer and, through appropriate treatment, reduce morbidity from the disease. Women in lower socioeconomic groups undergo pap tests less frequently (Kegeles et al.

Maun 1949; Graham et al. 1982; Graham 1986; Kreyberg 1938; Maisin and François 1928; Tannenbaum 1940, 1942; Tannenbaum and Silverstone 1953; Willett and MacMahon 1984; Willett et al. 1987; Wynder, Rose and Cohen 1986). Although the experimental evidence on the role of fat intake has been particularly impressive, the epidemiological evidence nevertheless remains in a state of flux. One difficult problem has been the accurate measurement of intake of dietary fat and specific dietary constituents in individual human subjects, especially over extended time periods. There are indeed socioeconomic gradients in diet and body weight. The issue here is whether such gradients could be quantitatively significant in explaining socioeconomic differences in breast cancer incidence and survival.

1965; U.S. Department of Health and Human Services 1983). There is little doubt that increasing use of pap smears has been important in the decline of cervical cancer.

Sex and Viruses. Individual sexual practices, gauged mostly by the number of different sexual partners, have been found to be an important determinant of cancer of the cervix (Terris and Oalman 1960; Wynder et al. 1954). The cancer, in fact, is rare among virgins. The most compelling explanation of this finding is that sexual contact transmits certain viruses, primarily human papilloma virus and herpes simplex virus-2 (Editorial 1987). The herpesviruses and certain other viruses have been increasingly implicated in the genesis of cancer in humans, particularly squamous cell carcinomas.[12]

Cigarette Smoking. Until recently, the epidemiological evidence on cigarette smoking in relation to cervical cancer was considered inconsistent. Within the past five years, however, there is increasing evidence of a potential role of cigarette smoking in the genesis of cervical cancer (Brinton et al. 1986; Winkelstein et al. 1984). While carcinogenic components of cigarette smoke are initially absorbed through the lungs, they have a wide bodily distribution outside the lung.[13] In fact, there is preliminary evidence for mutagenic compounds in the cervical mucus of cigarette smokers (Holly et al. 1986).

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12. See Austin et al. 1986; Bréchot et al. 1982, 1985; de Villiers et al. 1985; Schantz et al. 1986; Shillitoe et al. 1982; Smith et al. 1976; Trichopoulos et al. 1987; Winkelstein et al. 1984; zur Hausen 1982.

13. For example, cigarette smoking can cause bladder cancer; and in fact the bladder carcinogen 4-aminobiphenyl can be detected in the blood of cigarette smokers (Bryant et al. 1987), while mutagenic compounds can be detected in smokers' urine.

Synergistic Interactions. These three causal influences-- pap smears, viral infection and cigarette smoking-- need not act independently. In fact, there is good reason to think that they would act synergistically in the development of cancer.

Viral infection can result in the insertion of foreign DNA into the genetic material of the infected cell. This is one way that viruses are though to cause cancer in humans and other animals. Moreover, it has long been known that viruses could enhance the carcinogenic effects of tars (Rous and Kidd 1936, 1938). Viruses can also turn on and turn off the cellular markers that permit the body's immune system to recognize and attack growing tumors (Schrier et al. 1983; Tanaka et al. 1985). Still other agents can depress the ability of the natural killer cells in the immune system to attack the viruses themselves. When the body's system of cellular immunity is depressed, for example by cigarette smoking, then humoral system takes over, and increased antibodies to the virus are detected (Smith et al. 1976).

The notion of a biological synergism between viruses and cigarette smoking in the genesis of cancer is actually a special case of a much wider class of potential interactions between physicochemical agents and social and economic conditions. After all, there is little reason not to think of the failure to obtain pap smears as a social condition that interacts with the physicochemical agents. For many women, viral infection of the cervix through sexual contact and carcinogen absorption through cigarette smoking may have figured in the genesis of cervical cancer. Still, such women may not have exhibited clinically overt cancer had the lesion been identified at the preneoplastic or early neoplastic stages.[14]

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[14]. Excision of suspicious lesions that have been identified by cervical cytology is not the only way to stop the progression of an early cancer. Elective hysterectomy (as might be performed for uterine fibroids) is another means. To this end, we need to investigate whether elective hysterectomies

4. Malignant Melanoma and the Consumption of Leisure

We start with two observations. First, sunlight exposure appears to have a role in the genesis of malignant melanoma of the skin. Second, at least in developed countries, the incidence of melanoma appears to be directly related to socioeconomic status (Lee and Strickland 1982; Vågerö and Persson 1984). While there is substantial evidence to support the first proposition,[15] the socioeconomic gradient in melanoma deserves more careful scrunity.

In an analysis of melanoma cases in the United States, college education and high income were more prevalent (Williams and Horm 1977). In an Australian study, skilled and semi-skilled outdoor workers had lower rates than clerks and salesmen, who in turn had lower rates than the managerial and professional occupations. Women showed the same gradient in melanoma incidence when classified according to their husbands' occupations (Lee and Strickland 1980). In New Zealand, there was likewise a socioeconomic gradient in melanoma incidence, with production-transport workers having the lowest rates. Melanoma incidence appeared have little relation to outdoor/indoor

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are more prevalent among women in upper socioeconomic groups.

[15]. See Lancaster and Nelson 1957; McGovern 1952. Black persons and other pigmented races have a much lower incidence of the disease, with the exception of melanomas in less pigmented parts of the body, such as the sole of the foot and the mucosa of the oral cavity (McGovern 1977). In white persons, melanoma occurs predominantly on the sun-exposed parts, though the bodily distribution of tumors is not as consistent as that for other sun-sensitive skin cancers, e.g., basal cell cancers of the skin of the face and neck in white persons (McGovern 1952). Moreover, there is a general gradient of melanoma incidence in relation to latitude of residence, though the gradient is not limited to melanomas at sun-exposed body sites (Lancaster and Nelson 1957). Patients with the inherited disease xeroderma pigmentosum, who cannot repair ultraviolet light-induced damage to the DNA in their skin cells (Robbins et al. 1974), have a much higher risk of melanoma as well as other skin cancers.

work exposure (Cooke, Skegg and Fraser 1984). A Swedish study revealed a similar occupational gradient in melanoma incidence, but only for the covered parts of the body (Vågerö, Ringbäck and Kiviranta 1986).

Some investigators have concluded from such data that there is a genuine effect of socioeconomic status on melanoma incidence, independent of an effect of sunlight exposure. Others suggest that such effects are still somehow mediated by differential ultraviolet light exposure among various socioeconomic groups. For example, indoor, undiffused flourescent lighting might contribute to meloma in white-collar workers (Beral and Robinson 1981).

Recreational Tanning vs. Work-Related Sun Exposure. The dose-response relationships between melanoma incidence and sunlight exposure are, no doubt, more complex than for other skin-sensitive cancers. The critical question is whether intermittent recreational tanning, as opposed to prolonged work-related sun exposure, may have a different effect on skin melanocytes.

Some studies have suggested that melanoma incidence is related to cumulative sun exposure, both occupational and recreational (Holman and Armstrong 1984; MacKie and Aitchison 1982). But one large case-control analysis found that intermittent episodes of sunburn do pose a higher risk (Elwood et al. 1985). If so, then the hypothesis most consistent with the evidence is that outdoor work produces a protective tan on sun-exposed parts of the body. Further, the occupational gradient in melanoma incidence for the covered parts of the body would be an effect of intermittent, recreational tanning among upper socioeconomic groups. The fact that melanoma is found at much younger ages than other sunlight-sensitive skin cancers (McGovern 1977) may reflect a higher prevalence of recreational tanning among young persons.

I shall not dwell here on the evidence concerning recreational tanning among various social groups (Vågerö, Ringbäck and Kiviranta 1986). The critical point is that socioeconomic gradient in melanoma incidence may depend not only on work-related exposures, but also on the way in which leisure time is consumed. Analysis of the amount and content of leisure time may, in fact, have general application in the study of socioeconomic influences upon health. Consider, for example, the finding that certain types of leisure-time exercise, as opposed to work-related exertion, may be protective against coronary heart disease (Chave et al. 1978; Karvonen 1982).

5. The Multistep Nature of Cancer

I have hinted at "early stage" and "late stage" events in the genesis of breast cancer. I have also noted that viruses, cigarette smoking, and medical intervention can affect different stages in the development of cervical cancer. The dosing schedule of ultraviolet light that most predisposes to malignant melanoma, I have suggested, is the intermittent, high intensity exposure characteristic of leisure-time suntanning among persons of higher socioeconomic position. I now seek a more general framework for tying some of these ideas together.

The development of human cancer is a protracted, multiple-step process that evolves over years, if not decades, during an individual's lifetime. It is widely recognized that specific chemical and physical agents in the environment can affect the multiple stages of tumor evolution. My main point here is that social and economic conditions can likewise impinge upon various specific steps in the oncogenic process.

The concept of the multistep origin of cancer is often applied solely to the process by which a single cell develops into a biologically distinct tumor. Here, I employ the notion more generally to include the entire sequence of tumor generation, growth, detection, clinical progression, morbid evolution and, where applicable, recovery or death.

There is compelling evidence that at least the early stages of cancer development entail one or more alterations in the genetic apparatus of individual cells. The concept of "carcinogenic" or "cancer-causing" is sometimes applied solely to agents or host characteristics that influence such alterations in cell genes. Here, I refer also to those characteristics of the human host that may influence the rate of growth of the abnormal tumor cells, their differential survival advantage over normal cells, their metastatic spread to other tissues, or their susceptibility to medical interventions. Among such host characteristics are a person's occupation, diet, sexual behavior, allocation of work and leisure time, exposure to infectious agents, psychological stresses, as well as the timing and content of medical care.

The Early Stages of Cancer. Most if not all human cancers appear to begin with some damaging alteration in the genetic material of a single cell. Although such genetic alterations may not offer a full explanation of cancer, they are central to its genesis.[16]

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16. See Bishop 1987; Sager 1986. Through individual point mutations or large rearrangements in chromosomes, an error occurs in the replication of DNA, a highly faithful process that precedes the division of each parent cell into a new generation of cells. If the cell fails to repair the error in DNA or repairs it improperly, and if the error is compatible with continued cell life, then the damaging alteration is inherited by future generations of cells within the body.

There are several routes by which such genetic changes can be effected: by ultraviolet light from the sun, by ionizing radiation, by certain viruses, and by certain chemicals. In patients with primary cancer of the liver, for example, the DNA from hepatitis B virus has been found integrated within the normal genetic sequence of liver cells (Bréchot et al. 1982). In the case of chemical carcinogenesis, the damage to DNA is not necessarily caused by the chemical in the original form that it enters the body. Instead, it is very often a metabolite of the entering chemical, produced in specific organs, that is capable of reacting directly or forming an "adduct" with DNA and with other large molecules.[17] In fact, the specificity of certain carcinogenic chemicals to certain animal species and to certain human organs may be governed largely by variations in species and organ metabolism (Miller 1980).

Oncogenes. The alterations in DNA that initiate the cancerous process appear to be specific to certain genes, called "proto-oncogenes," which are critical in the regulation of cell growth and differentiation (Balmani 1985; Bishop 1987; Weinberg 1982). Many different and complex types of damage to the genetic material of cells can apparently turn a proto-oncogene into an abnormally expressed "oncogene."[18] Many such oncogenes have been discovered

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17. See Miller and Miller 1952. For example, the chemical carcinogen benzo(a)pyrene (BaP), identified in the 1930s (Cook et al. 1932, 1933), is metabolized to various "diol epoxides" that adduct with DNA (Brookes and Lawley 1964). Such adducts can be detected among coke oven workers exposed to BaP in the work atmosphere (Haugen et al. 1986). Likewise, the chemical 4-aminobiphenyl, a cause of bladder cancer to which certain occupations and cigarette smokers are exposed, is metabolized first to a "hydroxylamine" and ultimately to a form that can interact with the DNA in bladder cells. Measurement of the amount of the hydroxylamine of 4-aminobiphenyl that is bound to hemoglobin in human blood has been proposed as a precise method of gauging the carcinogen's exposure in cigarette smokers (Bryant et al. 1987).

18. For example, chromosomal breaks and rearrangements may shift proto-oncogenes away from their normal locations in the gene sequence, where the previously silent genes are then abnormally expressed (Rowley 1984; Sager 1986).

in human and other animal tumors. In fact, experimental models now exist in which specific carcinogenic chemicals produce specific mutations in specific proto-oncogenes, consistently yielding the same type of cancer (Bishop 1987).

It remains uncertain whether the expression of a single oncogene can alone be sufficient to initiate cancer development in humans. In some experimental settings, two cooperating oncogenes are required for the conversion to a "transformed," neoplastic cell (Land, Parada and Weinberg 1983). Such a finding is consistent with the notion, mentioned in the previous section, that very different genotoxic agents can interact in the production of malignant change. The finding of multiple oncogenes in many naturally occurring human tumors may also reflect the combined effects of various carcinogenic agents, encountered over a lifetime.

The likelihood that such compound genetic alterations will occur and be perpetuated appears to depend upon the rate at which cells are dividing (Borek and Sachs 1968). The rate of cell division may in turn be enhanced by nonspecific injuries to an organ. The idea is that nonspecific injuries stimulate tissue repair, which entails cell division. For example, in experimental studies, the effect of certain carcinogenic chemicals on liver cells is markedly enhanced by prior surgical injury of the liver (Kitagawa et al. 1980; Pitot 1982).

Although specific environmental agents may thus initiate the cancer process through genetic damage, the magnitude of their carcinogenic effects can depend upon other, possibly nonspecific characteristics of the human host. In principle, any nonspecific exposure or behavior that alters metabolism (e.g., alcohol's effect on liver microsomes) could in turn induce those

critical enzymes which convert specific chemical carcinogens into their active metabolites. In principle, nonspecific forms of tissue injury, again through nonspecific toxic exposures or environmental conditions, could accelerate cell division at susceptible sites and thus enhance the genotoxic effects of more specific agents. Thus, a number of nonspecific irritants or inflammatory processes in the lung could enhance the carcinogenic effect of cigarette smoking (Skillrud et al. 1986). Such mechinisms could underly the synergistic effect of asbestos exposure and cigarette smoking on the production of lung cancer. Moreover, the genotoxic actions of one agent could in principle potentiate the carcinogenic effects of another.[19]

Cancer Promotion and Progression. The genetic alterations that characterize the initial stages of cancer yield an irreversibly modified, "transformed" cell. The existence of a transformed cell, however, may be a necessary but not a sufficient condition for the development of a biologically distinct cancer. In some identified experimental instances, the expression of an oncogene creates only a "pre-cancerous" or "initiated" cell (Bishop 1987). Genuine malignant potential does not obtain until additional changes ensue.

There are two forceful arguments for the importance of such additional changes. First, there is a long-standing literature on the existence of pre-cancerous lesions in humans, ranging from the identification of leukoplakia as a pre-cancerous lesion of the oral cavity (Judd and New 1923) to the clinical diagnosis of early forms of cancer by cytological smears (Auerbach et al. 1957; Papanicolaou and Traut 1943, Papanicolaou and Koprowska 1951).

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19. Certain chromosomal aberrations induced by BaP are enhanced in asbestos-exposed smokers (Kelsey, Christiani and Little 1986).

Second, in a long line of animal experimentation, mostly through the application of such chemicals as tars to rodent and rabbit skin, investigators recognized how more benign-appearing papillomas and epitheliomas could later turn into more malignant carcinomas; they further recognized that sufficiently small doses of such tars could produce a pre-neoplastic state in which no tumors were apparent (Rous and Kidd 1941). Such experiments have been standardized into what is now called the "initiation-promotion" model (Pitot 1982).

The Initiation-Promotion Model. In the initiation-promotion model, a single application of an initiating chemical is followed by repeated applications of a promoting chemical. While the initiating agent alters the cells' genetic material irreversibly, the process of promotion is reversible.[20] Although the precise mechanisms of promotion are not fully elucidated, it appears that pure promotors do not initiate the early genetic changes of cancer. Instead, they may stimulate the growth of initiated cells, thereby rendering them more susceptible to further genetic change.[21]

Many investigators regard promoters as widespread in the human environment. Alcoholic beverages have been described as promoting oral, liver and esophageal cancer; asbestos as promoting lung cancer; saccharin as promoting bladder cancer; and synthetic estrogens as promoting adenomas of the

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20. The experiment produces cancer only if the initiator is applied first, and only if the promotor is applied subsequently in frequent, repetitive doses. Thus, BaP serves as an initiator in experimental liver cancer, while phenobarbital and PCBs serve as promoters. See Pitot 1982.

21. In some experiments in mouse skin, it appears that an initiating agent can cause a point mutation in a single proto-oncogene, yielding benign papillomas. The promoting agent then acts to enhance the expression of the abnormal oncogene, leading to malignant skin tumors.

liver (Pitot 1982).[22] Cigarette smoke is thought to contain both initiating and promoting agents.

Whether or not the experimental initiation-promotion model suffices to characterize the natural history of human cancer, there remains little doubt that the early genetic changes in pre-cancerous cells are part of a multi-component, protracted sequence of events, in which the emerging cancer acquires selective advantages over other normal cells, resists attack by the cellular immune system, becomes capable of proliferation and invasion of adjacent tissue, and ultimately metastasizes to distant organs. A more general term to describe such a sequence is cancer "progression."

Socioeconomic Influences on Cancer Progression. I suggest here that a number of nonspecific socioeconomic influences impinge upon cancer development during the progression phases. Two classes of socioeconomic influences will receive special attention below.

First, I focus sharply on what many authors have generally termed the "stress" of poor social and economic conditions, and the ways in which such stress may affect "host susceptibility" (Cassel 1976; Haan and Kaplan 1985; Haan, Kaplan and Camacho 1986; Marmot et al. 1987; Syme and Berkman 1976). I shall attempt to put in perspective what we currently know about the potential role of various types of social and economic stress on bodily immune defenses in cancer progression. Although there is a substantial experimental and clinical basis for a role of stress in cancer progression, we have very little

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[22]. As mentioned in footnote 10 above, prolactin, a human pituitary hormone whose secretion appears to be depressed by first pregnancies, is a promoter of breast cancer in animal experiments. Also, many gross aspects of nutrition, including fat, fiber, and caloric intake appear to have promotional effects. See footnote 11 above.

idea, I suggest, as to its quantitative importance, particularly in explaining socioeconomic gradients in cancer morbidity and mortality.

Second, I examine the interaction between socioeconomic status, medical care, and cancer progression. Although there has been considerable work on the determinants of seeking medical care, little has been done on the content of such care, or the manner in which social and economic factors may influence the effectiveness of cancer treatment.

6. Immunity, Cancer and Stress

There are numerous biological mechanisms by which the immune defensive system of the body could affect the genesis and progression of cancer.

First, the immune system conducts surveillance against viruses that may be oncogenic.[23] Second, in combination with certain mechanical defenses, the immune system influences the clearance of certain chemical complexes from the body.[24] Third, the immune sytem appears to have a role in recognizing and attacking newly transformed cancer cells. This is the most important and least settled area of inquiry.

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23. As mentioned in Section 4, the cellular immune system could be important in preventing the herpesvirus infections linked to cancers of the cervix and upper aerodigestive tract (Schantz et al. 1986).

24. Among such complexes are the "particulates" formed from the burning of cigarette smoke and fuels, such as the coke oven emissions mentioned in Section 5. While the carbonaceous core of such particulates may be chemically inert, the entire particle may contain reactive, potentially carcinogenic agents. The fate of the reactive compounds on such particulates may depend critically on the manner by which inhaled particles are cleared by the lung. Thus, clinicians have repeated observed how patients with lung cancer also have noncancerous chronic obstructive lung disease. It has been now been suggested that the concomitant, noncancerous lung disease actually sets up the lung for the subsequent development of cancer by impairing the clearance mechanism for carcinogenic particulates (Skillrud et al. 1986).

Roughly speaking, the immune system is designed to detect and neutralize "foreign" or "antigenic" material. The system of surveillance against antigens is highly regulated. Antibodies against the antigen are produced by B lymphocytes; the B lymphocytes are in turn stimulated by "helper" T lymphocytes; the helper T lymphocytes are in turn regulated by "suppressor" T lymphocytes. Certain "killer" T lymphocytes and other immune system cells also attack the target material, producing a number of substances that execute the attack. The killer T lymphocytes are in turn regulated by "suppressor" T lymphocytes. The overall state of the human immune response depends on the counterbalancing effects of these regulatory cells (Nossal 1987).

Accordingly, an external insult that disrupts T lymphocyte function need not result in depression of the immune response. An insult to the regulatory T cells could actually enhance the immune response (Herberman and Ortaldo 1981; Reinherz and Schlossmen 1980). Many acquired diseases of the immune system show both kinds of defects. The process of ageing is accompanied by progressive involution of the thymus gland, resulting in nonspecific deterioration of the entire T lymphocyte system ("immunosenescence"). While depressed aspects of the immune response in the aged could facilitate the initial establishment of tumor, the enhanced aspects could slow tumor growth. Such complex feedback effects have been invoked to explain why cancers occur more frequently but grow more slowly in older persons (Ershler 1986).

There is extensive experimental evidence that the immune system does indeed recognize some tumors.[25] Although some human cancers likewise express

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[25]. A particular mouse tumor, for example, can be made cancerous by one virus and rendered inactive by a cousin virus. The latter virus activates the cellular machinery to express an antigen that is in turn recognized by the immune system (Schrier et al. 1983; Tanaka et al. 1985).

antigens that could be recognized by the immune system, nevertheless a great many others-- at least at the stage of cancer in which they are studied-- do not appear to be "immunogenic." That is, the immune system no longer recognizes them as foreign (Ershler 1986). Such a finding, however, does not necessarily imply that the immune response was irrelevant; instead, such tumors, though initially immunogenic, may have undergone further genetic changes that removed the immunogenicity. On the other hand, there also experimental models in which the immune response appears to stimulate rather than attack tumors.[26]

A final difficulty is that the cancer, once established, can itself produce an immune deficiency syndrome. Accordingly, measurement of immune deficiencies among cancer patients need not imply that the deficiency facilitated the development of cancer. Just as some cancers produce hormones and other substances that cause wasting, hot flashes and other bizarre syndromes, so they can produce substances that upset the immune system.

Stress and the Immune System. It is well established that stress can impair the immune defense system. Although the mechanism probably involves the brain's mediating influence on the endocrine system, the details are sketchy (Borysenko and Borysenko 1982; Schair and Camerino 1976; Solomon, Amkraut and Kasper 1974). Stress can result in the production of certain steroid hormones that in turn cause at least temporary regression in the thymus gland.

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[26]. In at least some of these cases, T suppressor cells are turned on, thus inhibiting the killer cells that attack the tumor. In others, the immune response disrupts natural tissue barriers, allowing the tumor to spread.

There is both experimental and clinical evidence for the immunosuppressive effects of stress. In one experimental model, for example, daily exposure of mice to a "shock avoidance task" resulted in increased susceptibility to herpes simplex virus (Rasmussen et al. 1957; Rasmussen 1969). Among the stressors that appear to affect the immune response in humans are: space travel, sleep deprivation, physical trauma, imprisonment, loneliness, the stress of an academic examination, the death of a family member and other bereavements, psychiatric symptoms of anxiety and depression, marital disruption, and unemployment.[27]

It remains unclear whether such diverse environmental stresses have any characteristics in common. One possible feature-- variously termed "avoidability" or "escapability" in the experimental literature-- may correspond to what is termed "coping style" in clinical investigations (Laudenslager et al. 1983; Locke et al 1984; Pavlidis and Chirigos 1980; Sklar and Anisman 1979). Another is the prolonged, repetitive character of the stress. Immune impairment was not detectable until 9 months of continuous unemployment in a cohort of women (Arnetz et al. 1987). Marital disruption over extended periods likewise produced immune impairment (Kiecolt-Glaser et al. 1987).

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[27]. See Arnetz et al. 1987; Jacobs and Charles 1980; Glaser et al. 1985; Kiecold-Glaser et al. 1984, 1987; Locke et al. 1984; Shekelle et al. 1981. Such immune impairments have been measured by dimunition in killer T cell activity, ability to respond to standard skin tests for cellular immunity, impaired responsiveness of B lymphocytes to various chemical challenges, increased antibodies to EB virus (a particular herpes virus that causes mononucleosis), and DNA repair in certain lymphocytes (Kiecolt-Glaser et al. 1985).

Stress and Tumor Development. Stress can enhance the progression of pre-existing tumors in a number of experimental systems (Andervont 1944; Marchant 1967; Riley 1975; Sklar, Amkraut and Kasper 1974; Sklar and Anisman 1979; Sklar, Bruto and Anisman 1981). Although common features of such models are difficult to discern, considerations of escapable versus inescapable stress, and of acute versus chronic stress have been raised. In some models, isolation of experimental animals enhances tumors; in others, it inhibits them.

If the immune system can in principal influence tumor development, and if stress can affect the immune system in both the laboratory and the clinic, and if stress promotes oncogenesis in some experimental models, then can we not conclude that stress contributes to cancer in humans? Yes, but that is not the problem. The more difficult questions are: Even if stress can facilitate cancer progression, is the effect quantitatively important in humans? Can't we be more specific about the relevant characteristics of stress in humans? Do these characteristics have any bearing on the stresses frequently identified with certain social and economic environments? At this juncture, the epidemiologic and clinical evidence on stress and cancer has not afforded clear answers to these questions.

Psychological Stress and Cancer. There is an enormous, long-standing clinical literature on psychological stress and cancer.[28] Much of this literature makes the mistake of attempting to define a typical "cancer

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[28]. See Angell 1985; Casselith et al. 1985; Derogatis et al. 1979; Evans 1926; Green 1954; Greer et al. 1979; Jacobs and Charles 1980; Leshan and Worthington 1956; Pettingale, Greer and Tee Deh 1977; Renneker and Cutler 1952; West, Blumberg and Ellis 1952.

personality."[29] A number of papers have attempted to assess, mostly retrospectively, what psychological characteristics of newly diagnosed cancer patients appeared to improve survival. Although there is a general theme that patients with certain coping styles did better-- especially those who expressed anger and other feelings, as opposed to those who suppressed affect-- more careful studies suggest that such effects on survival may be small at best (Angell 1985; Casselith et al. 1985).

Epidemiology. Unfortunately, epidemiological investigations of stress and cancer have been sparse. Studies of cancer in relation to bereavement have provided mixed, circumstantial evidence (Ernster et al. 1979; Jones, Goldblatt and Leon 1984). In one prospective study, however, psychological depression was predictive of the 17-year risk of cancer, even when attempt was made to control for the potentially confounding effects of cigarette smoking, occupation, age, and alcoholic beverage consumption (Shekelle et al. 1981).

Studies of the stresses associated with lower socioeconomic status have pointed to marital disruption, low social mobility, job dissatisfaction, unemployment, social disorganization, "status inconsistency," and other factors. To the extent that such stresses are unavoidable and chronic, they appear to mimic those stress that facilitate cancer under more controlled conditions. To the extent that such stresses might be repetitively experienced over long periods but still reversible, they might act in ways similar to other oncogenic promoters. Despite the significant body of evidence that such stresses matter to some degree, we remain far from determining how much.

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29. Sontag 1977.

7. Medical Care: Quantity, Timing and Content

Substantial differences in the use of medical services among socioeconomic groups are well-documented and of long standing (Sydenstricker 1929). In the period before the introduction of widespread private and public health insurance in the United States, poorer persons generally had fewer doctor visits and hospitalizations.

Equalization of Health Care? Beginning in about 1950, however, and especially after the enactment of Medicare and Medicaid in 1966, the income-related gradients in physician visits, surgical rates, and hospital days per capita narrowed markedly in the United States (Bice et al. 1973; Bombardier et al. 1977; Freeborn et al. 1977; Newacheck et al. 1980; U.S. Department of Health and Human Services 1985; Wilson and White 1977). By 1980, with the noted exception of dental services, the income gradients for many medical services were either eliminated or actually reversed. We have some evidence, moreover, that the increased health insurance caused-- not just arrived coincidentally with-- the growth of medical care use by the poor (Shapiro et al. 1986).

Still, there is a reasonable basis for disputing the apparent trend toward equalization in medical care use among social classes. The comparisons generally involve crude rates; they do not always withstand attempts to take account of age or health status (Davis, Gold, and Makuc, 1981; Kleinman, Gold and Makuc 1981). Moreover, data on overall contact rates do not address differences in the content of medical care. They do not tell us whether there is still a disproportionate use of hospital clinics and emergency rooms among

black persons and the poor. They do not tell us who does and does not have a regular source of care (Dutton 1986).

The growth of health insurance had a clearly documented, nonspecific effect on the demand for medical care. However, there is surprisingly little evidence that such subsidies actually enhanced the use of medical services that are specific to cancer diagnosis and treatment.

Consider cancer detection. Income differentials in the use of Pap smears and self-examination for breast lumps appear to persist (U.S. Department of Health and Human Services 1985). Similar evidence on hemoccult tests for blood in the detection of colon cancer or on mammographic screening for breast cancer appears lacking.

Consider early seeking of medical treatment. While the proportion of localized breast cancers among newly diagnosed, elderly cases increased after Medicare (Friedman 1974), such a finding may have little to do with increased insurance among the elderly. In one study of Massachusetts breast cancer cases (Friedman, Parker and Lipworth 1973), there was no relation between the extent of insurance coverage and the clinical stage of the initial lesion.

Recent results from the Rand Health Insurance Experiment suggest that copayment affects only the decision to seek care for minor ailments-- not for such serious symptoms as exertional chest pain, loss of consciousness, significant involuntary weight loss, or nonmenstrual bleeding unrelated to nosebleeds or minor trauma (Shapiro et al. 1986). In this study, subjects were selected to overrepresent black and lower income persons. It was striking that the proportion of subjects seeking a physician for any particular serious symptom was only on the order of 20 percent.

What was once an enormous, burgeoning literature on the determinants of delay in cancer treatment[30] appears to have gone out of fashion after the advent of medicare and medicaid. Yet evidence on persistent differences in the proportions of localized cancers among white and black patients at least suggests that delay remains a serious problem.

The literature on delay in cancer was part of a much larger inquiry: why people seek medical care; whether they follow the medical advice they have received; what are their values and beliefs concerning the efficacy of treatment or the degree of personal control over health; how decisions to seek care are influenced by mass communications and lay referral networks.[31] Except for studies of patient compliance, which deal primarily with conformance to outpatient medication regimens, this literature appears to offer little insight into potential differences in the content of care among persons of varying social and economic position.

The Content of Medical Care. I have already documented significant socioeconomic gradients in cancer survival, even when patients with the same clinical staging have been compared.[32] These differences persist when reasonable adjustments are made for differences in noncancer death rates. While clinical staging imperfectly reveals tumor virulence, we cannot dismiss

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30. See Bates 1948; Cobb et al. 1954; Goldsen, Gerhardt and Handy 1957; Kutner, Makover and Oppenheim 1958; Leach and Robbins 1947; Pack and Gallo 1938; Robbins et al. 1950; Robbins, Macdonald and Pack 1953.

31. See Becker et al. 1972, 1974; Becker and Maiman 1975; Blackwell 1973; Caldwell 1970; Cowles et al. 1963; Deasy 1956; Finnerty et al. 1973; Gordis, Markowitz and Lilienfeld 1969; Gray, Kesler and Moody 1966; Janz and Becker 1984; Kegeles et al. 1965; Macdonald et al. 1963; Pill and Stott 1982; Rodin 1986; Rosenstock et al 1959; Rosenstock 1966; Sackett 1978; Svarstad 1986; Watts 1966.

32. See also Dayal and Chiu 1982; Nomura et al. 1981; Pendergrass, Hoover and Godwin 1975; Wegner et al. 1982.

the possibility that the content of cancer care differs meaningfully among persons of vary social position.

Data from the SEER program (Axtell, Asire and Myers 1975) show that the proportion of white leukemic patients (both acute and chronic) receiving some definitive therapy (chemotherapy, surgery, or radiation) increased from 50% in 1950-54 to 75% in 1970-73; the proportions among black leukemic patients were 64% in 1950-54 and 76% in 1970-73. For acute lymphocytic leukemia, a curable childhood disease, the proportions definitively treated were: 67% in 1950-54 and 95% in 1970-73 for whites; 77% in 1950-54 and 96% in 1970-73 for blacks. It remains uncertain whether the SEER data, which derive in significant part from university medical centers, are representative of overall white-black differences. Nor it is clear whether such white-black differences apply to other indicators of socioeconomic status.

Socioeconomic Status and the Doctor-Paient Relation. The literature on delay in cancer, especially in the 1920s and 1930s, was especially concerned with the distinction between physician versus patient "culpability" for delay. In the parlance of analysis of variance, we might now term these "patient-specific effects" and "physician-specific effects." The former category reflects concerns, which have been repeatedly voiced in the literature, that patients do not comply with prescribed regimens, or that other unspecified characteristics of the host environment influence the efficacy of cancer treatment. The latter category reflects differences in quality of care.

Adherence to our statistical terminology requires that we also consider "patient-doctor interaction effects." There has been some sporadic interest in the social distance between the upper class doctor and the lower class

patient (McKinlay 1975; Stoeckle 1987). Still, we do not know whether recent changes in the demographic mix of graduating physicians could indeed have affected the content of care among minorities and others in lower social strata.

8. A Research Agenda

Can documented differences in reproductive history among women of various socioeconomic groups explain quantitatively the observed differences in breast cancer incidence? Can they explain the differences in severity of cancer at the time of initial diagnosis?

Although there is a substantial literature on the economic and social determinants of marriage and fertility (Montgomery and Trussell 1986), much work remains to be done on the timing of the first birth. Historically, there have been marked differentials by income, education and race in the age of first full-term pregnancy; but these patterns may have radically changed with the advent of oral contraceptives in the 1960s and the continued influx of women of all social strata into the labor force. Although economists and demographers have attempted to fashion mathematical models of the timing of first birth and subsequent birth intervals (Heckman, Hotz and Walker 1985), these have been mostly descriptive. We really do not have a clear theoretical model of birth timing.

Although epidemiological studies have examined the quantitative relation between reproductive history and breast cancer, they have been performed without attention to the determinants of reproductive history. We know that early first birth influences breast cancer incidence. From separate studies,

we know that income, education and race also influence breast cancer incidence and survival. We need to studies these determinants of cancer together.

How do specific sexual practices vary across social strata? Have differences in such indices as the number of different sexual partners annually diverged over time? How will such trend impinge upon future cervical cancer rates?

Even in the relatively short interval between initial writing and revision of this paper, the public concern about the sexual transmission of human immunodeficiency virus has risen dramatically. There is serious concern that the virus is spreading by heterosexual means, particularly among persons of lower socioeconomic status. Yet our understanding of the problem is seriously hampered by a general lack of information on sexual practices among various social and economic groups. And the difficulty applies just as well as to studies of the relation between sexually transmitted viruses and cancer.

Can we amass detailed information on the use of cervical pap smears by various social groups, assessing recent trends?

Despite numerous studies on the use of medical care among various social and economic groups, we need to focus more sharply on preventive measures. We need to know more clearly whether insurance coverage or non-price factors are critical in the use of pap smears, mammography, stool blood analyses and the like.

How do leisure-time sun-tanning practices vary among socioeconomic groups in the United States? Do the results accord with current evidence on melanoma indicence?

In Section 4, I did not directly confront the question of the empirical relation between social status and leisure-time tanning. While there is indeed some evidence that upper income people have more frequent high-intensity bursts of sun exposure, this empirical regularity needs more careful study. Even if there was a socioeconomic gradient in the past, it may now be changing. The issue is not trivial. While basal cell epithemiola (the most prevalence form of sun-related skin cancer) is usually not fatal, malignant melanoma is.

If nonspecific chemical and physical toxins can accelerate initiation of cancer, and if we suspect that such toxins are more prevalent in poorer environments, then how do we identify such agents?

This is an extraordinarily difficult research question. For if nonspecific insults did matter, then studies to identify isolated chemical spills, water contamination, occupational exposures and the like would identify only a small fraction of the cancer that might be related to lower social status. One possible approach is to examine those localities with a persistently elevated incidence of certain cancers. Do the residents in such places have lower incomes and education? How often can the elevated cancer incidence be attributed to specific, identifiable carcinogens? Except for a few case studies, we seem to be a long way from this end.

Could molecular epidemiologic studies, based upon measurements of adducts to macromolecules, permit us to say more about differences in early stage carcinogenesis among varying social groups?

This is indeed a promising area for further research. But first we have to widen the array of agents that can be detected in such molecular studies.

Once this biological research is further advanced, we will want to know how adduct levels relate to income, education, occupation, sexual behavior and other characteristics.

What epidemiologic studies are needed to delineate the quantitative effect of social and economic stresses on cancer progression?

At this writing, I can identify only one prospective cohort analysis to assess the predictive value of psychological depression on subsequent cancer incidence (Shekelle et al. 1981). But depression, as measured by standard questionnaires, may be a poor indicator of social and environmental stress. Without additional long-term cohort studies, the role of stress in human cancer will remain speculative.

What field studies are needed to assess differences in the content of cancer treatment among various socioeconomic groups?

Even after the advent of Medicare and Medicaid, we are still not in a position to assess the content of cancer treatment among various educational and income groups. We need to know much more about the content of such care. Do poorer patients receive curative chemotherapy or adjuvant chemotherapy? Are chemotherapy or radiation treatment terminated earlier? Do patients in different social strata tolerate the side effects of such treatments to different degrees? How much do doctors explain to their patients about cancer? How does the message vary with doctor and patient? Is the phenomenon of doctor-patient mismatch important? Has the growing supply of minority physicians affected the care and treatment of cancer among minorities?

Much of the required research will require a detailed analysis of the actual course of cancer care among cohorts with different socioeconomic

characteristics. In this case, we will be asking not whether poorer people have lower cancer survival rates, but why they fare so poorly. Much of the favorable clinical data on various cancer treatment regimens comes from controlled studies of defined protocols in selected populations. We don't really know whether these protocols are actually followed in non-study populations. If they are not, we don't know why not.

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