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A STUDY TO DETERMINE THE EVOLUTION OF ADVANCES IN MEDICAL TECHN--ETC(U)
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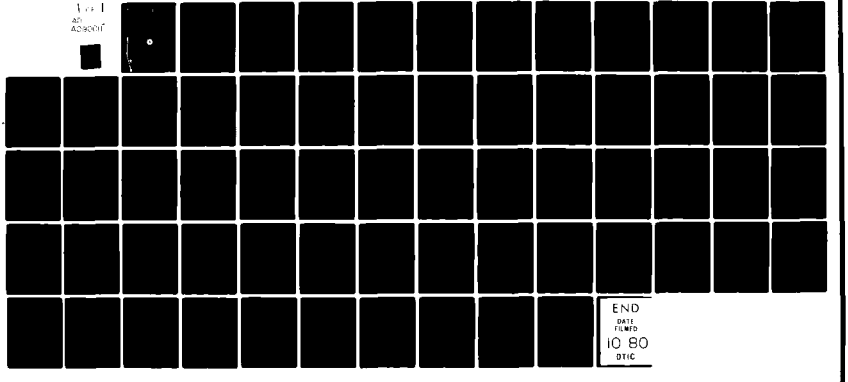

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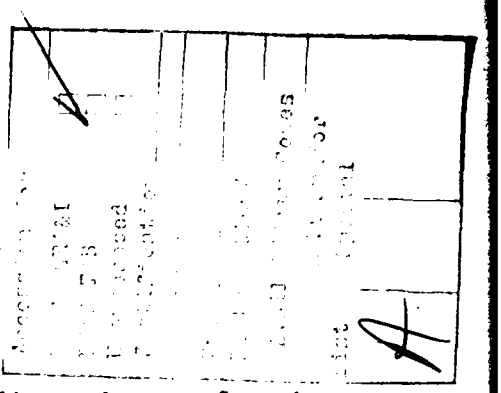

MEDICINE: THE 20-YEAR OUTLOOK

Introduction

About one million people in the United States die each year from heart disease. While effective chemotherapy exists for many heart diseases the suddenness of heart attacks often precludes their use. Preventive therapy and better screening hold the best promise for reducing the death rate due to heart disease. Improved diagnostic procedures and technologies are rapidly being developed, but many of these remain inaccessible to those without adequate medical care.

Some of the new diagnostic technologies and procedures now in use include detection recording and analysis of magnetic impulses generated by movement within the heart, a urine test to detect myoglobin, echocardiography (both 1- and 2-dimensional), stress testing, blood enzyme tests to spot minor heart attacks, displacement cardiography, doppler shift cardiography, ballistocardiography, and portable electro-cardiograph equipment for heart patients to wear to identify premature ventricular contractions and other episodic arrhythmias. Some diagnostic procedures under study include minute devices which can be implanted in or wrapped around a vein or artery to measure the flow of blood, radioactive scan tests to detect dying cells in the myocardium, radioactive tests to measure cardiac output and the left ventricular ejection fraction, and cardiac biopsy techniques for diagnosing and following the course of cardiovascular disease.

High blood pressure (hypertension) is the most common cardiovascular disease. This is again an area where risk factors are identifiable. Effective chemotherapy has been primarily responsible for controlling blood pressure

and slowing the death rate from this disease. High blood pressure's secondary effects, however, are still largely unarrested; these include kidney failure and stroke.

For those patients with known heart disease the need for more advanced technology is apparent. Research has shown that the electromagnetic environment is increasing in magnitude due to new electrical and electronic devices, sophisticated medical equipment, and high powered radars. It is therefore necessary that such technologies as implantable cardiac pacemakers be imperious to these changing situations. Heart valves with integral sensors soon may be available which permit computer monitoring of blood flow.

Research in the past year has yielded a number of promising cardiovascular chemical agents, including dobutamine-crocetin, to increase oxygen diffusion and prevent arteriosclerosis, and RO2-2985 (a streptomyces-derived drug) to guard against hemorrhagic shock and congestive heart failure. On the non-chemical side biofeedback and yoga techniques have been used in the remediation of hypertension.

The most popular open heart operation—the coronary artery bypass graft (CABG)—has come under attack in recent months. About 28,000 CABG operations are performed annually, but the impact of CABG on future heart attacks and premature death still is disputed. Some surgeons have stated that drugs and other medical care constitute better forms of treatment for angina pectoris.

Many risk variables have been documented in the past. These include heredity, sex, race, and age. Risk factors that can be changed, either by treatment or by the victim himself, are serum cholesterol level, high blood pressure, diabetes, cigarette smoking, diet, stress, and exercise. Some risk factors thought to be responsible for heart disease still are in dispute.

The most common type of stroke--the occlusive stroke--represents the culmination of progressive vascular disorders existing for many years: this implies the possibility of prediction. Other risk factors include hypertension, obesity, and ECG abnormalities. A major study performed by Edward Freis in the 1960's showed that fewer incidents of stroke were found in those populations with controlled hypertension. A history of transient ischemic attacks (TIA's) is another indicator of significance. Vascular reconstructive surgery aimed at improving the brain's blood supply can be performed to stave off probable strokes. This surgery also has been performed with good results after strokes have occurred.

Angiograms are given to nearly all patients at risk, but the procedure is somewhat dangerous as well as time consuming. Two non-invasive screening tests, thermometry and opacity pulse propagation measurement, are currently being evaluated.

A large part of stroke injury may be due to imbalances in secretion of neurotransmitters in the brain. Two researchers have recently offered this theory to explain some of the least understood symptoms of stroke, e.g., apparent dysfunction of brain areas far removed from the site of vascular damage. Drugs now are available to correct these imbalances in patients suffering from psychotic depression, Parkinsonism, and schizophrenia. Perhaps these drugs may find some application in reversing damage and by restoring the balance in stroke survivors.

Many researchers believe that the outcome of a stroke may be altered in the first 72 hours, before infarction and edema damage sets in, i.e., before there is irreversible destruction of neural tissue not destroyed immediately by the original trauma. A team of neurologists from the Bouman Gray School of Medicine use advanced monitoring and therapeutic procedures to maintain

adequate cerebral circulation during this crucial period. The National Institutes of Health is now supporting research into stroke acute care research units.

Further innovations include refinements of present ultrasonic tools, intracranial pressure monitoring, and computerized soft tissue tomography. Special emphasis will be placed on non-invasive procedures.

MORTALITY RATES

Deaths from heart disease rose 18 percent between 1940 and 1963 but have declined since then more than 10 percent. Health officials statisticians are cautiously optimistic that the "epidemic" is under control. For the first time since 1967 deaths from coronary heart disease fell below 1 million in 1975. This decline has occurred particularly among middle-aged white men, and this trend is forecasted to continue. Many observers conclude that the fall is not due to improved treatment of heart attack but to greater emphasis on controlling hypertension and a decline since 1968 in mortality from influenza and pneumonia (since these two diseases are known to influence the coronary death rate). This view is supported by evidence that the decrease in death rates has occurred primarily in the winter months, February through November, the peak months for respiratory disease mortality.[1] U.S. health officials have attributed the drop in mortality to media campaigns to better educate the public about hypertension and smoking, and to improved methods of diagnosing and treating cardiovascular diseases.

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[1] "A Decline in Coronary Mortality," British Medical Journal, No. 6001 (January 10, 1976), p. 58.

Most recently the role of coffee drinking in heart disease has been questioned. Since the publication of Dr. Oglesby Paul's classic 1973 study, many research projects have endeavored to prove a correlation between coffee drinking and heart disease. The Boston collaborative drug surveillance program has reported a survey showing a greater heart attack risk among coffee drinkers. The Kaiser-Permanente Medical Center published a study in October 1975 which suggests other factors associated with coffee drinking—personality, national origin, occupation, and climate—may in fact be responsible for the differences in heart disease rate.

Several food staples have been accused of promoting heart disease: margerine may be responsible for arteriosclerosis, homogenized milk perhaps reduces artery wall elasticity, salt has long been known to be involved in hypertension, and conversely soft (low mineral content) water also may help produce hypertension. A number of studies have shown that high cholesterol diets appear to promote heart disease. A study reported by Joseph L. Goldstein indicates that one out of every five persons suffering a heart attack had a possibly genetically caused elevated blood fat condition.

Interestingly the anticlotting factor in aspirin may prove to be a preventative for heart attacks. The National Heart and Lung Institute is sponsoring an Aspirin-Myocardial Infarction study to determine whether such a correlation exists.

Stroke kills more than 200,000 Americans each year and leaves many more totally or partially disabled. Yet stroke has not been attacked as vigorously or as successfully as heart disease or cancer. Most practitioners have believed that stroke damage is irreversible and cannot be prevented. But new leads have opened in stroke research.

DIAGNOSIS

Coronary artery disease now is thought to begin in childhood rather than in middle-aged adulthood, so screening and treatment may be extended to children and adolescents in the future. In autopsies of black and white males and females aged 15 to 19, between 71 and 83 percent showed fatty streaks in coronary arteries and raised atherosclerotic lesions were found in 7 to 22 percent.[2]

Laboratory tests and clinical procedures are available which identify accurately traits associated with increased risk of coronary disease. Not all persons with symptoms of coronary disease will die from it, and half of those who do will never have exhibited symptoms. Procedures to identify patients at risk have become more sophisticated and reliable and the improvements outlined below are expected to further refine diagnosis of the nation's leading cause of death.

To date much of the criticism of diagnostic techniques for arteriosclerosis has been directed at its high cost versus benefit. Until reliable treatments are established and it can be shown that the course of the disease can be halted or reversed, the value of expensive and time-consuming diagnosis is debatable.

Physicians now are able to look directly at the blood vessels and clearly see lipid deposits. Angiograms and arteriograms are procedures with relatively small risk in well equipped hospitals, but they are somewhat complex and not likely to be routine. (In recent months some critics have charged that too many hospitals are performing angiograms on too many patients.

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[2] J. P. Strong and H. O. McGill, Jr., "The Pediatric Aspects of Atherosclerosis," Journal of Atherosclerotic Research, Vol. 9 (1969), pp. 251-265.

These practitioners believe that the operation is a research technique and should not be used so frequently.) New, non-invasive tests soon may become available to allow physicians to look directly inside the arteries and to check periodically whether treatment programs are reducing the size of deposits or increasing them. For the first time a physician actually will be able to follow a patient's progress resulting from specific treatments. For example, a system developed at the University of Southern California utilized a computerized digital image processing system by which plaques are made visible by injecting special dyes which are opaque under X-rays.[3]

Conventional X-rays of the heart are unsatisfactory because they are not clear and are difficult to read. In addition the contrast medium injected into the heart to render it opaque flows out of the heart in a short time.

Ultrasound is now often used as an alternative to catheterization of the heart to detect heart valve damage, infections of coronary tissue, benign tumors, embolisms, and birth defects. In echocardiography sound waves reflected from the heart are used to form an anatomical illustration of the organ.

An ultrasonic camera now under development in England would allow cardiologists to watch a moving picture of a cross-section of the heart in fine detail and thus avoid the need for catheterization for many common diagnostic purposes. The camera's resolution is believed to be 5 to 10 times superior to existing devices.

If a patient survives a heart attack doctors are unlikely to be able to modify the size of the damaged heart muscle to prevent another infarction. A new test developed at the Washington University School of Medicine measures

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[3] H. M. Schmeck, Jr., "Hardened Artery Shown in Picture," New York Times (December 31, 1973), p. 17.

an enzyme released from damaged heart muscle—creatine phosphokinase—to determine whether the damage is extensive and if it is increasing in size.[4] Another diagnostic test measures protein myoglobin in the urine by radial immunodiffusion assay. Higher levels of urinary myoglobin are associated with more massive damage to the heart muscle.[5]

Radioactive minerals also are likely to be important in diagnosing damage in the future. These agents, particularly thallium-201 and technetium-99m pyrophosphate, concentrate in normal heart tissue only. When viewed from outside the body with a scintillation camera, damaged heart muscle areas appear as " old spots," allowing the physician to estimate location and extent of infarct damage. Combinations of radioactive agents can even distinguish between regions of recent and older heart damage.[6]

Electrocardiograms have been in use for several years to measure heart performance. Exercise EKG's—walking on a treadmill or bicycling on a stationary device while hooked up to an EKG—enable physicians to detect more problems. One physician estimates that resting EKG's detect single-vessel coronary disease about 15 percent of the time, while the Masters two-step test (in which a person is monitored while taking one step forward and one step back) is 35 percent accurate. Proponents of stress testing report a 93 percent reliability of that technique to detect single-vessel problems

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[4]"Medicine: Help for Heart Patients," Newsweek (February 4, 1974), p. 58.

[5]"Diagnosing Severe Heart Attacks," Science News, Vol. 105, No. 23 (June 8, 1974), p. 367.

[6]M. S. Donsky, et al., "Unstable Angina Pectoris: Clinical, Angiographic, and Myocardial Scintigraphic Observations," British Heart Journal, Vol. 38, No. 3 (March 1976), pp. 257-273.

and 85 percent for severe heart disorders. Even without the EKG linkup anginal pain is a good indicator of disease with stress testing.

A new pharmacologic test may be simpler to perform with less stress to the patient: dipyridamole is injected intravenously to induce anginal pain. If the pain ceases after aminophylline is administered the test is said to be positive. Early studies indicate this procedure to be at least as reliable as exercise EKG's.[7]

Tests for high levels of blood fats traditionally have been costly and require fasting prior to the test. New York's Rockefeller University has developed a new screening method known as the heparin turbidity test, which is technically simple and inexpensive. If blood fat levels are shown to be excessive patients will still need to undergo the more sophisticated procedure to determine which specific fats are responsible so that diet or drugs can be initiated.

Arrhythmia patients are most likely to die of "sudden death" heart attacks than any other group, and the cardiac arrest is preceded by premature ventricular contractions. Easy to wear portable monitors would be ideal for these ambulatory patients and Survival Technology, Inc., has developed a cigarette package-sized monitor (the "CardioBeeper") for this purpose. The patient transmits his heartbeat to a doctor via telephone for advice. However, first year sales of the device have not been significant.

Although it represents a leading cause of death, stroke in all its forms has received little attention in clinical practice. Many hospitals still classify acute stroke victims as hopeless and often administer no treatment at all.

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[7] M. Tauchert et al., "New Pharmacologic Test for Diagnosis of Coronary Artery Disease," Deutsch Med. Wochenschr, Vol. 101 (January 9, 1976), pp. 35-37.

Traditionally angiograms have been used for diagnosing cerebrovascular disease. The procedure is expensive and time-consuming, and there is some risk to the patient. As alternatives, simpler and non-invasive screening methods now are under study. Opacity pulse measurements and thermometry have been shown to be useful in deciding whether arteriograms should be taken.

A new technique for diagnosing stenosis (narrowing) of the carotid artery offers many advantages over arteriography. Phonoangiography, a non-invasive, less costly procedure, is likely to reduce the number of arteriograms and to encourage greater testing for arteriosclerosis. Phonoangiography uses a pressure-sensitive microphone to record artery sounds; these sounds are analyzed by computer. Speed of blood flow within the artery combined with the computer analysis of pitch and loudness allow the physician to estimate the diameter of the carotid artery.

Arteriography has been the only accurate method of detecting fatty deposits blocking the carotid blood vessels to the brain. Scientists at the Cleveland Clinic Foundation have reported success with a safer technique called carotid compression tomography. Changes in blood flow through the carotid arteries are reflected by pressure changes inside the eye. The test measures eyeball fluid pressure while mild pressure is applied manually to the carotid artery. The rapidity, safety, and ease of this new procedure will enable more extensive screening of the patient population at risk of stroke.

THEORIES

Artherosclerosis is the primary cause of death in the United States and Western Europe, yet its cause and pathogenesis remain unknown. The disease progresses insidiously over a period of years before symptoms emerge. The

early development of the disease is therefore not observed, and conclusive identification of risk factors remains difficult. Much of the research in artherosclerosis focuses on risk factors associated with clinical symptoms (hyperlipidemia and hypertension in particular) although some effort has been directed to chemical and structural characteristics of the lesions observed at autopsy or in animal models. Very recently research has been aimed at the pathobiology of the arterial wall and the role of smooth muscle cell growth in lesion formation.[8]

Risk Factors Associated with Clinical Symptoms

Beginning with the Framingham study data on risk factors in coronary heart disease have been compiled so that physicians can control these clinical manifestations and it is hoped reduce incidence of the disease. Hundreds of large-scale epidemiologic studies have been performed to elucidate those risk factors. Two of the most important projects are the Framingham study and the Multiple Risk Factor Intervention Trial.

The Framingham study was one of the first and largest epidemiologic studies to illuminate risk factors in coronary heart disease. The 25-year research effort has uncovered many of the factors believed to be associated with cardiovascular disease. As physicians become more aware of these factors they are able to identify patients likely to develop coronary heart disease and begin preventive treatment. Because therapy can, in many instances, reduce or eliminate certain risk factors (hypertension, lipid levels, cigarette smoking, obesity, diabetes) researchers are hopeful that individuals prone to heart disease will live longer. This belief is currently being tested by the National Heart and Lung Institute's Multiple Risk Factor Intervention Trial (MR. FIT). This large-scale study with its

[8] R. Ross and J. A. Glomset, "The Pathogenesis of Atherosclerosis—First of Two Parts," The New England Journal of Medicine, Vol. 295, No. 7 (August 12, 1976), pp. 369-375.

participating 20 clinical centers will assess the impact of certain preventive measures on the rate of heart failure. This research effort involves 12,500 males and is expected to be concluded by 1982 at an annual cost of about $12 million. The selected volunteers have no clinical evidence of coronary heart disease but they are at higher than average risk of developing it because of elevated serum cholesterol levels, hypertension, or cigarette smoking, singly or in various combinations. These three risk factors were selected for intervention studies because each can be effectively reduced or eliminated. Half of the participants will enter a special program to decrease or do away with one or more of these factors through changes in lifestyle and medical treatments. In six years researchers believe that conclusive evidence will exist which will help to prevent heart attacks and premature deaths in at least one segment of the U.S. population.

Hyperlipidemia

Epidemiologic studies have established an association between high concentrations of serum cholesterol and increased risk of heart attack. Yet researchers continue to argue that the relationship may not be causal. The Coronary Drug Project, sponsored by the National Heart and Lung Institute, undertook a nationwide study in 1966 to answer this question. Enrolled in the program were 8300 men who had experienced one or more heart attacks. Two drug regimens known to lower serum cholesterol were tested in patients for a period of five to eight years. Both drugs achieved slight reductions in serum cholesterol levels (an average of less than 10 percent), but neither reduced significantly deaths in contrast to patients taking placebos. Side effects of both drugs included heart arrhythmias and thus researchers concluded that the benefit-to-risk ratio for using cholesterol-reducing drugs was not favorable in men who had suffered at least one heart attack. Researchers are quick to point out, however, that this study should not be used to reach conclusions

about the use of cholesterol-lowering agents in preventing first heart attacks. Perhaps by the time a heart attack has occurred, slight reductions in serum cholesterol levels are no longer beneficial.[9] Other studies now in progress may establish conclusively the role of cholesterol in primary prevention.

Dietary cholesterol has become suspect in heart disease for a number of reasons:

- Atherosclerotic plaques contain large amounts of cholesterol and its esters.
- Individuals with high serum cholesterol levels are at greater risk of developing arteriosclerotic complications than those with lower serum cholesterol levels.
- Diseases such as nephrosis associated with elevated serum cholesterol levels are also associated with pronounced arteriosclerotic lesions.
- Feeding cholesterol to some mammals induces cholesterol deposits in many tissues, including the arteries.[10]

Other research contradicts the link between cholesterol and heart disease:

- There is often no correlation between extensive arteriosclerotic disease at autopsy and premortem cholesterol values.[11]
- Some human groups (e.g., the Masai, the rural Swiss) have diets high in saturated fats but maintain low serum cholesterol levels and have a low incidence of coronary heart disease.[12]

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[9] J. L. Marx, "Coronary Project: Negative Results," Science, Vol. 187, No. 4176 (February 14, 1975), p. 526.

[10] H. Kuanitz, "Dietary Lipids and Arteriosclerosis," Journal of the American Oil Chemists Society, Vol. 52, No. 8 (August 1975), pp. 293-297.

[11] Ibid.

[12] M. J. Hill, "Metabolic Epidemiology of Dietary Factors in Large Bowel Cancer," Cancer Research, Vol. 35, No. 11, Part 2 (November 1975), pp. 3398-3402.

One researcher even asserts that generalizations based on saturation are worthless because various saturated fatty acids each have different effects on serum cholesterol levels.[13] With respect to the Masai and rural Swiss the kinds of saturated fatty acids in the diet could be responsible for lower cholesterol levels, as could intake of dietary fiber and other diet variables.

The effect of exercise on serum cholesterol levels and prevention of atherosclerosis has long been debated. A recent study examined the effects of exercise on specific lipoproteins and found that exercise reduces the level of lipoprotein fractions which are believed to be responsible for the disease. Thus while exercise does not reduce overall serum cholesterol levels, it appears to be beneficial in decreasing serum triglycerides.[14]

Meal frequency also may have an effect on cholesterol levels and heart disease. Feeding experimental animals one meal a day has been shown to promote higher serum cholesterol levels than frequent feedings. Furthermore, a study of 1133 men, ages 60 to 64, found that ischemic heart disease was significantly more frequent among those who ate three meals a day or less than among those who ate five or more meals.[15]

Fried foods were listed as a variable in a 1963 study of smoking in relation to mortality and morbidity, but the study surprisingly turned up a negative correlation between the death rate and ingestion of fried food. The actual figures are presented below.

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[13] H. Kuanitz, "Dietary Lipids and Arteriosclerosis."

[14] "Exercise: Of Benefit in Heart Disease?" Medical World News, Vol. 15, No. 40 (November 22, 1974), p. 46-F.

[15] M. C. Moore, et al., "Dietary-Atherosclerosis Study on Deceased Persons," Journal of the American Dietetic Association, Vol. 67, No. 1 (July 1975), pp. 22-28

Table 1

AGE STANDARDIZED DEATH RATES PER 100,000 MAN-YEARS, MEN AGED 40-69[16]

FRIED FOOD	NON-SMOKERS	SMOKERS
None	1208	2573
1-2 times per week	1004	1694
3-4 times per week	642	1714
5-9 times per week	781	1520
10-14 times per week	722	1524
15+ times per week	702	1783

While ingestion of saturated fat may be causing health problems for some people, it also is possible that the cures for these problems are themselves contained in fats and oils. Polyunsaturated fats have a cholesterol lowering effect that has turned the attention of some researchers to the ratio of polyunsaturated to saturated fats in our diets. The cholesterol lowering effect becomes significant at a p/s ratio of slightly over 1/1. The sitosterols removed from soybean oil in refining have been used to lower serum cholesterol levels.[17] There is even some medical evidence to support sales of garlic oil capsules to lower cholesterol levels.

The action of fatty acids on cholesterol levels differs from acid to acid, but the addition or lack of other nutrients in the diet complicates the picture. The B vitamin, inositol, is one of the substances that helps counter the effect of cholesterol in the arteries; it also is one of the nutrients that is removed from our bread in processing and is not restored.[18] Some researchers theorize

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[16] E. C. Hammond, "Smoking in Relation to Mortality and Morbidity," Journal of the National Cancer Institute, Vol. 32, No. 5 (May 1964), pp. 1161-1183.

[17] T. J. Weiss, Food Oils and Their Uses (Westport, Connecticut: Avi Publishing Company, 1970).

[18] G. Marine and J. Van Allen, Food Pollution (New York: Holt, Rinehart, and Winston, 1972).

that sugar is responsible for creating imbalances which hinder the body's ability to break down fats. The increasing per capita consumption of refined sugar has been positively correlated with the increasing incidence of coronary heart disease.

High triglyceride levels as well as elevated cholesterol levels are associated with heart disease. Triglycerides, however, are hard to measure accurately and are subject to many influences. For instance, females have been found to maintain lower triglyceride values than men on the same diet, but women using oral contraceptives were found to have significantly higher triglyceride levels than those not on the pill.

A high fat intake has been reported to shorten blood clotting time. One study shows that feeding arachidonate (arachidic acid occurs naturally in small amounts in soybean, corn, peanut, safflower, olive, and palm oils) to human subjects increases the sensitivity of their blood platelets to aggregation.[19] In another study when dietary fat consumption was decreased to 25 percent of total calories consumed for a 40-day period, systolic blood pressure in healthy men and women declined significantly.[20]

Another theory suggests that the deposition of cholesterol in the arteries may occur initially in response to some chemical or mechanical damage to the artery wall, possibly caused by excess serum cholesterol itself. Chronic hypercholesterolemia then is seen as a condition that repeatedly irritates

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[19]"Dietary Essential Fatty Acids, Prostaglandin Formation, and Platelet Aggregation," Nutrition Reviews, Vol. 34, No. 8 (August 1976), pp. 243-246.

[20]J. M. Iacono, et al., "Reduction in Blood Pressure Associated with High Polyunsaturated Fat Diets That Reduce Blood Cholesterol in Man," Preventative Medicine, Vol. 4, No. 4 (December 1975), pp. 426-443.

the damaged artery wall and prevents its healing as well as contributes to the build-up of atherosclerotic lesions.[21]

While the research attempts at elucidating the problems of cholesterol intake and heart disease are by no means conclusive, our society is tentatively moving toward dietary control of fats. The customary diet in the United States obtains 40 to 45 percent of its calories from fat with a polyunsaturates to saturates ratio of about 0.3/1 and 500 to 750 milligrams of cholesterol. The American Heart Association and Intersociety Commission on Heart Disease recommend that less than 35 percent of total calories come from fat and that of these less than 10 percent are from saturated fat. They also recommend a cholesterol intake of less than 300 milligrams per day.[22]

One approach to the problem of excessive saturated fat in the American diet is to alter the desirability of or accessibility to beef. A return to grass-fed cattle has been advocated as a means of saving grain and energy as well as to lower the fat content of beef. The fat in cattle feed also can now be protected from the hydrogenation it usually undergoes in the steer's rumen.[23]

Norway has begun a national program to lower total fat intake by establishing a more favorable polyunsaturated to saturated ratio. In doing so the government had to weigh the nutritional benefits against reverses to its dairy industry, a vital part of the economy. But it has done so with a full awareness of good nutrition and necessary economics. In other countries one

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[21] R. Ross and L. Harker, "Hyperlipidemia and Atherosclerosis," Science, Vol. 193 (September 17, 1976), pp. 1094-1099.

[22] C. Jansen, J. Dupont, and G. G. Blaker, "A Tool for the Individualized Management of Fat-Controlled Diets," Journal of the American Dietetic Association, Vol. 6[illegible] No. 1 (July 1975), pp. 78-85.

[23] R. E. Hodges, et al., "Plasma Lipid Changes in Young Adult Couples Consuming Polyunsaturated Meats and Dairy Products," American Journal of Clinical Nutrition, Vol. 28, No. 10 (October 1975), pp. 1126-1140.

government agency tries to educate the public to change its eating habits while another works to support the industry whose products are being condemned as unhealthful.

There is nothing to indicate that the United States will move from the recommendations of a private association regarding fats and oils to a national fats and oils policy (consider our lack of an energy policy in spite of the crisis level impetus). Indeed the motivation for doing so may be lessened by a change in the direction of heart research away from such clinical manifestations as hyperlipidemia.

Hypertension

Hypertension is a major cause of complications leading to death in middle-aged and older persons and is the leading cause of death among blacks. Most of these deaths are preventable by long-term treatments yet many hypertensives are unaware that they have the disease and many patients, once diagnosed, are not motivated to continue treatment.

Life insurance companies have identified hypertension as one of the most important risk factors in premature death. Premium rates are usually higher for hypertensives, but this situation may be changing. Today some insurance companies are offering standard premiums to hypertensives who are receiving therapy under supervision of their physicians. The patient thus is provided with a monetary incentive to continue therapy.

Hypertension is the only risk factor which all clinicians and researchers agree can be modified with beneficial results. It is one of the best predictors of cardiovascular disease, often more so than cigarette smoking or serum cholesterol.

The American Heart Association estimates that only about half of the 23 million Americans with hypertension are aware that they have high blood pressure, and only half of these persons are under treatment. Of those receiving treatments many are not getting the proper therapy. Thus the potential for growing numbers of physician visits is evident.

Many physicians themselves are not aware of hypertension's significance: many believe that mild high blood pressure need not be treated; some physicians still do not seek out the disease but think that hypertensive patients will come to them with symptoms. Only 11 percent of doctors recently surveyed in England always measure blood pressure of middle-aged patients. Thirty-six percent of physicians believed that hypertensive patients exhibit symptoms such as vertigo, headache, nervousness, and insomnia. Screening programs have received considerable attention recently as local and national groups attempt to make the public more aware of this disease. Some community health specialists have criticized this program, arguing that many screening groups are unable to perform crucial follow-ups. The 1973 New Orleans project, for example, found 38 percent of 30,000 persons screened were hypertensive but followed up on only 5 percent. Follow-up should be done almost immediately: when more than a week elapsed between screening and verification, half of the patients did not return.

It has generally been thought that national health insurance will bring hypertension under control since more persons will be screened and will receive medication to treat high blood pressure.

Personality and Stress

Two San Francisco researchers have associated risk of heart disease with personality traits. Type A behavior pattern is aggressive, ambitious, competitive, and has a chronic sense of time urgency. The more relaxed Type B

subject has lower coronary heart disease incidence and less basic atherosclerosis.[24] A ten-year study of Japanese-Americans confirms these findings. The Japanese culture, according to sociologists, has built-in buffers to guard against personal stress. Traditional Japanese live in closely knit groups and have considerable stability in their lives; the group rather than the individual is emphasized. This could explain why Japan has the lowest rate of coronary heart disease of any industrialized nation.[25]

Most researchers acknowledge that behavior patterns play a role in coronary heart disease but do not believe it to be the most important cause. Because behavior patterns are difficult to alter on a widespread scale, most physicians continue to emphasize control of other well-established risk factors such as hypertension, hyperlipidemia, and cigarette smoking. Some critics of the behavior theory charge that it oversimplifies a complex issue and that personality typing is difficult if not impossible.

Physical Activity

Medical opinion remains divided on the effects of physical activity on heart disease in middle-aged and young men. The mechanisms by which exercise influences coronary risk is unknown, although it may be related to serum cholesterol levels.

A 22-year study of longshoremen on the West Coast has found that repeated short bursts of strenuous work or exercise over a period of years reduces the risk of fatal heart attacks.[26] In a study by the Irish Heart Foundation heavy

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[24] R. H. Rosenman, "Coronary Heart Disease in the Western Collaborative Group Study," Journal of the American Medical Association, Vol. 233, No. 8 (August 25, 197_, pp. 872-877.

[25] "Less Stress in Traditional Japan," Science News, Vol. 108, Nos. 8 & 9 (August 23 & 30, 1975), p. 125.

[26] R. S. Paffenbarger, Jr., and W. E. Hale, "Work Activity and Coronary Heart Mortality," The New England Journal of Medicine, Vol. 292, No. 11 (March 13, 1975).

leisure activity was associated with lower mean serum cholesterol levels and blood pressure. The level of exercise at work did not appear to influence this negative association, so that physical activity itself does not seem to be responsible for the lower risk-factor levels. This study team suggests that men who are physically active in their leisure time may smoke less and eat more wisely because of cultural or psychological reasons. Or perhaps men in better health generally are inclined to take more exercise.[27]

Cigarette Smoking

Cigarette smoking repeatedly has been associated with increased risk of cardiovascular disease. The Framingham Study shows that men who smoked when the study began but subsequently stopped experienced only half as many heart attacks after 18 years as their counterparts who continued to smoke. Similar conclusions were drawn from the 8-1/2-year study of 300,000 veterans by the National Heart and Lung Institute survey of over 1 million persons.

Cigarette smokers may be more susceptible to heart attacks caused by arterial thrombosis because nicotine accelerates the activity of platelets. Nicotine also increases heart rate, cardiac output, blood pressure, and coronary blood flow.

Coffee Drinking

The Framingham study has implicated coffee drinking as a risk factor in developing coronary heart disease, but more recent evidence refutes this observation. Newer studies have shown that cigarette smokers tend to be coffee drinkers, so the relationship is complicated by the addition of the known risk factor, nicotine. Other traits associated with coffee drinking

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[27] N. Hickey, et al., "Study of Coronary Risk Factors Related to Physical Activity in 15,171 Men," British Medical Journal, No. 5982 (August 30, 1975), pp. 507-509.

(including personality, national origin, occupation, and climate) also may be responsible for the association uncovered by the Framingham study.[28]

Coffee easily could be believed to be a risk factor because of the circumstantial evidence: caffeine raises blood pressure, interferes with sleep, elevates plasma levels of free fatty acids, and causes disproportionate increases in blood glucose levels among diabetics.[29] In a recent study with matched controls, however, the risk of death from coronary heart disease associated with coffee drinking is quite small for low-risk and middle-risk patients.[30]

Drinking Homogenized Milk

Drinking homogenized milk has been implicated in a subgroup heart disease caused by depleted plasmalogen in cell membranes, including arteriosclerosis, myocardial infarction, and angina pectoris. One hypothesis states that ingesting homogenized cow's milk leads to absorption of active xantine oxidase in the stomach and this enzyme is then deposited in the myocardium. This leads to breakdown of plasmalogens and depletion of tissue fatty aldehydes which results in myocardial damage. This hypothesis has gained favor because of increased death rates from coronary artery disease after widespread use of the homogenization process in the 1930's and 1940's.

Countering this theory is evidence that death rates began rising before homogenization and have fallen off in recent years although milk processing

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[28]T. R. Dawber, W. B. Kannel, and T. Gordon, "Coffee and Cardiovascular Disease," The New England Journal of Medicine, Vol. 291, No. 17 (October 24, 1974), pp. 871-874.

[29]S. Vaisrub, "A Break for the Coffee-Break," Journal of the American Medical Association, Vol. 231, No. 9 (March 3, 1975), p. 965.

[30]C. H. Hennekens, et al., "Coffee Drinking and Death Due to Coronary Heart Disease," The New England Journal of Medicine, Vol. 294, No. 12 (March 18, 1976), pp. 633-636.

remains unchanged. Many researchers question that xanthine exodase in homogenized cow's milk is absorbed intact and that it can remain biologically active in human tissue.[31]

"Soft" Water

Epidemiologists have long been puzzled as to why persons living in areas with low mineral content drinking water have a higher risk of heart attack than persons in hard water areas. If a causal relationship exists between water composition and heart disease mortality, then the responsible factor either must be a toxic substance in the soft water or a beneficial substance in the hard water. Calcium and magnesium are mostly responsible for the hardness of water supplies, and their absence correlates strongly with mortality rates. A 1974 study of water supplies in 194 American cities finds that the deaths in soft water areas could not be attributed to the presence of toxic substances or to a deficiency of essential trace metals but to the corrosive properties of soft water. This water tends to pick up harmful substances in corroded household plumbing, particularly while the water stands overnight. The first water drawn in the morning may contain heavy concentrations of cadmium, a hypertensive agent.[32]

Interestingly, investigators have established that the opposite relationship exists among residents of Kansas City, Kansas, and Kansas City, Missouri: the Kansas citizens use hard water and have a much higher cardiovascular death rate than their soft water neighbors in Missouri. This reversed pattern has allowed researchers to investigate other water-related correlations

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[31] E. L. Bierman and R. E. Shank, "Homogenized Milk and Coronary Artery Disease: Theory Not Fact," Journal of the American Medical Association, Vol. 234, No. 6 (November 10, 1975), pp. 630-631.

[32] "Water and Heart Disease: The Harder the Deadlier?" Medical World News, Vol. 15, No. 34 (October 11, 1974). pp. 45-46.

for the first time. Cadmium was found in hard water in levels three times higher than in soft-water areas. The ratio of cadmium to zinc levels (which acts as a hypotensive in cadmium-induced hypertension) was important here also.[33] A London researcher argues that the population studied in Kansas was too small. Dr. Fiona Stanley is part of a research group evaluating the hard water-soft water situation in 60 million people over 25 years. She notes that associations are established between water hardness and various elements in many countries but no one element can be shown to be universal: in the United Kingdom they believe calcium is responsible, and in Ontario researchers believe magnesium is most important.[34]

Serum concentrations of magnesium and calcium have been measured but no differences were found between soft water and hard water users. Yet the magnesium factor remains a popular theory since:

- Western diets barely supply sufficient amounts of magnesium.
- Concentrations of magnesium in the myocardium of persons suffering a myocardial infarct are abnormally low, suggesting that a low concentration of the element may predispose to myocardial infarct.
- Cardiac arrhythmias result when experimental animals are deprived of magnesium.

A study of magnesium concentration in the myocardium found that residents of hard water areas had significantly higher levels than those in soft water areas. There were no important differences between the two areas in myocardial concentrations of calcium, zinc, copper, chromium, lead, or cadmium.[35] Thus

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[33] M. L. Bierenbaum et al., "Possible Toxic Water Factor in Coronary Heart Disease," The Lancet, No. 7914 (May 3, 1975), pp. 1008-1010.

[34] Ibid.

[35] T. W. Anderson et al., "Ischemic Heart Disease, Water Hardness, and Myocardial Magnesium," Canadian Medical Association Journal, Vol. 113, No. 3 (August 9, 1975), pp. 199-203.

water-borne magnesium may protect against ischemic heart disease. Another study found magnesium/potassium concentration ratios in ventricular muscle samples to be lower in soft water areas than in hard water areas,[36] again confirming that magnesium deficiency in soft water areas may increase the risk of death after myocardial infarctions.

Transient Ischemic Attacks

Occlusive strokes, the most common form of cerebrovascular disease, might be reliably predicted in the future. Epidemiologic research has uncovered a number of risk factors including severe hypertension, obesity, elevated hematocrit levels, ECG abnormalities, and transient ischemic attacks (TIA's). While the etiology and preferred means of treating TIA's (or "little strokes") have not been established, TIA's are very significant in pointing out patients at risk. One third of all patients who experience a major stroke have a history of TIA's. Because TIA's are characterized by temporary neurologic dysfunction (such as dizziness) many attacks go unreported or misdiagnosed as more common conditions (e.g., migrains, epileptic discharge).

PATHOBIOLOGY OF THE ARTERIAL WALL AND PROLIFERATION OF SMOOTH-MUSCLE CELL GROWTH

Response to Injury Theory

A group at the University of Washington School of Medicine suggests that when the intima (the thin inner layer of an artery wall) is damaged, the smooth muscle of the artery wall is exposed to blood plasma--liproproteins

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[36] B. Chipperfield et al., "Magnesium and Potassium Content of Normal Heart Muscle in Areas of Hard and Soft Water," The Lancet, No. 7951 (January 17, 1976) pp. 121-122.

are the component of blood probably responsible--and cell proliferation is promoted. This hypothesis is essentially a third-generation extension of Rudolf Virchow's theory (circa 1856) that cell growth in the arterial wall begins with variation of the arterial intima.[37]

The Monoclonal Hypothesis

Another group of pathologists at the University of Washington has theorized that artherosclerosis begins with a single mutated cell, the formation of tumors in the arteries (possibly caused by carcinogens or a genetic susceptibility) which then accumulate fatty materials from the blood. Drs. Earl and John Benditt suggest that dietary fat and cholesterol thus probably play only a secondary role in the development of atherosclerosis. Benditt's research has indicated that all the cells of a single plaque appear to be derived from a single cell.[38] Many researchers have raised objections to this interpretation of the Benditt's research. However, there is evidence that plaques develop in layers, with underlying cells dying and only a few remaining cells proliferating in each layer. If this is correct, a plaque layer might consist of cells of a single enzyme genotype even though the plaque originated from many cells.[39]

The Clonal-Senescence Hypothesis

A third theory has been suggested by other researchers at the University of Washington. This hypothesis is based on Hayflick's observation of skin

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[37] R. Ross and J. A. Glomset, "The Pathogenesis of Atherosclerosis --Second of Two Parts," The New England Journal of Medicine, Vol. 295, No. 8 (August 19, 1976), pp. 420-425.

[38] Ibid.

[39] G. B. Kolata, "Atherosclerotic Plaques: Competing Theories Guide Research," Science, Vol. 194, No. 4265 (November 5, 1976), pp. 592-594.

cell replications: cells replicate a limited number of generations and this number is inversely related to the age of the donor. Martin and Sprague propose that atherogenesis is related to declining stem-cell activity in the arterial media. The intricate feedback system which maintains equilibrium in the cell population of the arteries (the large smooth-muscle cell population being supported by a small number of proliferating stem cells) begins to fail with aging, these researchers suggest. Dying smooth-muscle cells are no longer adequately replaced, intimal stem cells increase, and smooth-muscle cells accumulate in atherosclerotic plaques.[40]

This hypothesis is of interest because it relates directly to aging, a predominant risk factor in atherosclerosis.

Treatment

DRUGS

Lipotropics and Cholesterol Reducers

An eight-year nationwide collaborative study of post-myocardial-infarction patients has found that chances for survival or suffering future attacks are not reduced by prescribing lipid-lowering drugs such as clofibrate and niacin. Project Director Jeremiah Stamler emphasizes that the study's conclusions cannot be generalized to include patients who never suffered a heart attack. The very remote likelihood of influencing the course of the disease once severe atherosclerosis and heart damage have set in is probably why the cholesterol-reducing agents were shown to be ineffective.

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[40] R. Ross and J. A. Glomset, "The Pathogenesis of Atherosclerosis —Second of Two Parts."

Studies with the drug cholestryamine (now used medically to remove bile acids) suggest that it actually reverses the atherosclerotic process in monkeys. While the findings do not necessarily apply to older, calcified plaques, cholestyramine could play an important role in the treatment of early atherosclerosis in the future.[41]

Diuretics and Hypotensives

Drugs to control hypertension have been available since the 1950's. Those who take these drugs are at lower risk of developing cardiovascular disease than other hypertensives. The ongoing Veterans Administration Cooperative Study on Hypertensive Agents coordinated by Martin Edwards Freis has shown that lowering even mild hypertension is beneficial. Since the majority of hypertensives are not now treated with drugs, the implications of this finding are significant: uncontrolled and untreated mild hypertension should be greatly reduced in the future.

Some patients have not followed therapy because of side effects produced by drugs and because they do not perceive their condition to be "better" than before. The usual method of treating hypertensives is a "step-care" regimen. Patients are first treated with a thiazide diuretic. If necessary this is supplemented with a sympathetic blocking drug and finally a vasodilator, if needed. Newer drugs with improved benefits may eliminate the long trial period necessary to establish a treatment program. In some patients treatment does not reduce blood pressure to normotensive levels, yet even partial reduction has been shown to help in preventing cardiovascular

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[41] "New Drug for Atherosclerosis," Science News," Vol. 108, No. 22 (November 29, 1975), pp. 340-341.

complications. Treatment, once begun, usually is life-long, although sometimes drug dosages may be reduced.

Diuretics are expected to remain the most important agents for treating nearly all cases of hypertension. Diuretics act by decreasing the amount of sodium in the body which in turn leads to reduced water in the body. Thiazide diuretics most commonly are used in chronic diuretic therapy because they are well tolerated, can be absorbed completely from the gastrointestinal tract, and are moderately potent. Nearly all patients requiring diuretics are able to take thiazides; only those with renal function below 20 percent of normal require other diuretics. Loop diuretics have a different site of action than the thiazides. Furosemide, one member of this potent group, is prescribed more often than any other single diuretic agent, although many clinicians and academicians believe that it is not as effective in hypertension treatment as the thiazides. Treatment with furesemide is almost four times as costly as thiazide equivalent treatment. As cost considerations become more important to the physician (through the implementation of Maximum Allowable Cost and Professional Standards Review Organizations) use of these agents can be expected to decline somewhat. For some conditions, of course, fast-acting loop diuretics will continue to be preferable: severe cardiac failure, chronic renal failure, or when potassium supplementation cannot correct thiazide-induced hypokalemia.

Triamterene and spironolactone, the distal tubular diuretics, are less potent than the thiazides. These agents do not cause a loss of potassium; in fact, hyperkalemia is a serious side effect of the distal nephron diuretics. Mercurial diuretics rarely are used today because of the widespread availability of effective oral diuretics.

Hpotensive drugs have become less widely used in the wake of evidence linking reserpine to increased risk of breast cancer. Diuretics usually are preferred because of fewer side effects and better patient compliance. Availability of sustained-action dosage forms of hypotensives with low side effects probably would shift treatment away from diuretics, but such products are not likely to be introduced in the near future.

Anti-Arrhythmics

An arrhythmia is any electrical activity of the heart that is not a normal sinus beat. The causes of arrhythmias include electrolyte changes, drug toxicity, ischemia, rheumatic heart disease, and congenital defects.

Anti-arrhythmics are likely to be administered in emergencies to restore normal heart rhythm but not as a prophylactic. These drugs have several potentially hazardous side effects including depressed heart function due to changes in spontaneous heart rate, lowered blood pressure, and reduced heart muscle contractility and heart output. A newly synthesized drug which may prevent as well as correct arrhythmias and which is believed to have no significant effects on heart performance has been developed at the University of Michigan Medical School. Beta-blocking drugs have been used for many years to treat ventricular and atrial arrhythmias with fewer side effects.

Anti-arrhythmic drug failure occurs frequently because of inadequate levels of the drug in the blood and because of toxicity.

Anti-Platelets/Vasodilators

A 1953 study indicated that heart disease death rates were significantly lower for rheumatoid arthritis patients who used aspirin four or more days weekly than for non-aspirin users. More recent studies at Boston University and in England have encouraged the National Heart and Lung Institute to

initiate a long-range study of the effectiveness of chronic aspirin use in preventing heart attacks. Other drugs to be used prophylactically in the future might include prostaglandins and anticoagulants. This type of agent probably will first be used to treat patients with thromboembolytic or cerebrovascular disease but may ultimately be used widely in coronary vasodilation as well.

NON-DRUG TREATMENT

In patients with acute coronary insufficiency, medical (i.e., bed rest and drugs) treatment usually is advised initially. Coronary artery bypass graft (CABG) operations are undertaken in patients who do not respond to the medical regime and continue to experience disabling angina pectoris. The controversy surrounding the overuse or underuse of CABG is not likely to be resolved for many years. As one researcher has pointed out it is literally impossible to conduct a double-blind scientific study on this subject. Indications for the surgery probably will become more refined in the future, with fewer operations as a result. Even if CABG becomes the treatment of choice for some coronary patients, coronary vasodilators are not likely to be abandoned since they are helpful in keeping these grafts open and clear.

Probable strokes may be prevented or postponed through vascular reconstructive surgery designed to improve the supply of blood to the brain. A new surgical development allows blood flow to be re-established not only in the accessible arteries of the neck but in the intracranial vessels themselves. The procedure, developed in the mid-1960's, makes use of an operating microscope so that surgeons can anastomose very small arteries. The technique has been shown to be feasible in several hundred cases. Studies

are underway to demonstrate its clinical value and to develop criteria for selecting appropriate patients.

Better management of acute stroke is emphasized in many hospitals and emergency facilities today with the goal of re-establishing blood flow to the affected area. Drugs are used for much of this therapy. Current practice calls for anticoagulants to aid in routing blood to the brain. Other researchers are exploring the possibilities of reducing the brain's need for blood. Drugs such as barbiturates, when administered and monitored carefully, might be used in the future to reduce the oxygen requirements of affected tissues.

Recent research by two neuroscientists supports the theory that much stroke injury is caused by imbalances in the brain's neurotransmitters. When cells are starved of oxygen as a stroke occurs they die and release stored dopamine. The sudden flood of this chemical acts to spread the stroke's damage. This theory has little scientific support but is consistent with the clinical etiology of stroke damage. Drugs now are available to restore neurotransmitter balance in patients with psychotic depression, schizophrenia, and Parkinson's disease. These researchers are hopeful that similar drugs administered after a stroke can retard or reverse the damage.

CANCER

Introduction

Theories of the cause of cancer deal with a variety of processes. Some focus on the transformation of normal cells into cancerous ones. For example, viruses may alter a cell's genetic record so that its descendants become cancerous; various mutagens, chemical (e.g., colchicine) or physical (e.g., radiation) may do the same. Induction of cancer may be a two-stage process in which not only is there a change in a cell clone's DNA record but also a change in its identifiability by the body's immunological defenses, i.e., cells that contain altered DNA may occur all the time but may be quickly destroyed by the body's immunological defenses. Cancer may result when such a cell somehow becomes immunologically invulnerable.

Cancer cells often are oxygen-starved, since they typically live in a region of rapidly growing, high metabolic rate tissue. Therefore, cancer cells are unusually dependent on anaeroebic enzymatic processes. A switch to such dependence on fermentation-like processes may be a key step in the transformation of normal cells to cancer.

Other theories are concerned with the growth and spread of cancerous tissue. For example, cancers sometimes spread so rapidly that it is hard to credit their spread to descent from a single parent cell. Rather it would seem that some infectious, possibly viral, process communicates from cell to cell.

Over 300,000 persons die each year of malignancies. Industrialization probably has increased the number and amount of carcinogens in the environment, and artifical preservatives in foodstuffs also may have increased

exposure to carcinogens. If carcinogens present in the environment (including the atmosphere and in foodstuffs) were identifiable, a diagnostic test such as a urine test for cancer mutagens[1] would indicate "danger" areas and lead to earlier detection and treatment.

Of course some mutagens are not readily removed from the environment because individuals prefer to seek them out. For example, although the link between smoking and cancer has not yet been firmly agreed upon by all researchers, if it can be assumed that the link exists, continuance of smoking behavior means more cancer deaths. Nevertheless, cigarette smoking is forecasted to remain at present levels due to increased smoking incidence among youth and women.

Although diagnostic procedures have improved markedly, they are still not available to some persons. If multiphasic screening becomes more prevalent, or if a national health care plan is instituted, more potential cancer victims will be detected and treatment, where it exists, begun. For example, cancer of the colon in the past has been detected at a very late and usually terminal stage. If persons in the risk group (age 40 and over) were to receive annual proctosigmoidoscope examinations, the condition could be treated earlier.

Recent research has focused on the possibility of carcinogenic viruses. Many animal and bird cancers have been shown to have viral etiologies. If such viruses are indeed responsible for the evolution of human neoplasms, and these viruses can be identified, treatment or prevention by vaccines will be possible. Leukemia research has yielded very good results. Strong

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[1]"A Urine Test for Cancer Mutagens," Science News, Vol. 105, No. 17 (April 27, 1974), p. 278.

evidence exists that some form of virus is responsible, but other factors (environment, genetic predisposition) apparently also lay a major role in this disease.

Some research with the drug hydrazine sulfate has promising implications, although the effects have not yet been clarified. Chemists at Pennsylvania State University have discovered four new alkaloid derivatives which may prove useful in cancer therapy. Two researchers in Harrow, England, have developed a new and more efficient means of manipulating cells to be used in cancer therapy.

Clinicians are encouraged by results from combination drug therapy. Today 35 cancer drugs with FDA approval for use exist and at least four new antitumor agents probably will clear the FDA this year. Rifazone 8 may prove to be an effective agent in destroying malignant cells without harming healthy ones.

Spontaneous cancer regression is being studied for clues to cancer therapy, but the mechanism, or mechanisms, responsible remains unknown.

Immune therapy still is experimental but is emerging as a particularly promising approach. Chemicals such as dinitrochlorobenzene and biologicals such as BCG tuberculosis vaccine are capable of stimulating body defense mechanisms believed to be man's natural guard against cancer. A significantly stronger than normal anticancer immune response can be induced by exposing cancer cells to glutaraldehyde.

Diagnosis

Available tests to detect early cancer range from self-administered (breast self-examination, "seven warning signals" of the American Cancer

Society) to techniques requiring special training such as colonoscopy, mammography, colposcopy, and proctosigmoidoscopy. Some tests can be administered by primary care physicians in office settings: Pap test, breast examination, digital exam for rectal tumors, and the guaiac stool test. No breakthrough providing a simple chemical or immunologic test is expected for several years.

Later sections of this chapter will discuss other, newer diagnostic techniques: analysis of family background and immuno diagnosis.

SERUM ASSAYS

More than 100 serum assays have been suggested as cancer markers, but less than 10 have been proved to be predictive, and none are cancer specific. A new "B-protein" assay developed at the University of Tennessee appears promising although Mayo Clinic researchers doubt whether it would be sensitive or specific enough to detect preclinical tumors.[2] An experimental blood test discovered by a team of American and German cancer researchers may identify cigarette smokers whose genes make them prone to cancer.[3]

A complex day-long blood test has been developed in Ohio which may be 88 percent accurate in detecting common cancers; if further tests confirm this validity such a test might be used in some patients at risk.[4] The leukocyte adherence inhibition test seems to detect the presence of early

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[2]"Simple Blood Test for Cancer Developed," Chemical and Engineering News, Vol. 54, No. 39 (September 20, 1976), pp. 25-26.

[3]L. K. Altman, "Blood Tests Point to Smokers with Genetic Tendency to Cancer," New York Times (November 19, 1973), p. 42.

[4]"Study Shows Cancer Test 85 Percent Reliable," Chemical and Engineering News, Vol. 54, No. 3 (January 19, 1976), pp. 6-7.

cancers and helps to monitor and identify specific tumor antigens on the cell surface.[5]

URINE TESTS

Biochemists at the University of California have devised a simple urine test to detect a high percentage of environmental mutagenic chemicals. The test can be used to detect mutagenic metabolites of drugs and dietary components.[6] Other urine tests use dye to differentiate malignant from benign cells, antibladder antibodies to test for bladder cancer, and the presence of fibrinogen degradation products in the body.

CARCINOEMBRYONIC ANTIGEN TESTS

Carcinoembryonic antigen (CEA) tests appear quite promising in detecting some cancers. In 1974 the Food and Drug Administration (FDA) licensed the CEA for commercial availability in the United States as an adjunctive aid for the detection and management of cancer. False-positive results have been obtained in some healthy patients (cigarette smokers, patients with nonmalignant disorders) so the test is not recommended for general screening.[7]

California researchers report that a new subspecies of CEA is a more reliable test for gastrointestinal tumors, lung and breast cancer, and kidney

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[5]"Oncology: Blood Test for Early Ca," Medical World News, Vol. 17, No. 4 (February 23, 1976), pp. 6-7.

[6]"A Urine Test for Cancer Mutagens," Science News, Vol. 105, No. 17 (April 27, 1974), p. 278.

[7]"FDA Approves CEA Assay Kit for Cancer Management Diagnosis," FDA Drug Bulletin (January 1974), pp. 2-3.

disease. Primary liver cancer, stomach cancer, and testicular cancer may be detected by alpha-fetoprotein studies.[8] Studies of tests measuring levels of the enzyme histaminase may help to identify patients with small-cell lung cancer and to monitor effectiveness of treatments for this cancer. Further research may lead to routine use of such a test in patients at risk.[9]

The Makari Intradermal test measures skin reaction to an antigen-antibody complex injection. The test is still under evaluation, but it may prove useful in certain high risk groups as an initial screening for early cancer or recurrence of the disease.[10]

PHYSICAL CELL EMISSIONS

A new experimental cancer detection system positions the patient in a nuclear magnetic resonance chamber. Radio signals distinguish cancerous from normal tissue, since atoms from the cancer cells serve as transmitters with distinct wavelengths.[11]

A laser system to identify cancer cells has been found to be faster and perhaps more accurate than the traditional Pap test. So far the system has

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[8]"Some Tests More Promising Than Predictive," Medical World News, Vol. 17, No. 24 (November 1, 1976), p. 32; N. Zamcheck, H. Z. Kupchik, and G. Pusztaszeri, "CEA-S: A More Specific CEA?" New England Journal of Medicine, Vol. 293, No. 3 (July 17, 1975), pp. 145-146.

[9]"A Marker for Lung Cancer," Science News, Vol. 108, No. 13 (September 27, 1975), pp. 198-199.

[10]"The Makari Test: Successful Detection of Cancer," Scrip, No. 207 (May 29, 1976), p. 15.

[11]S. V. Jones, "New Patents: Cancer Found Electronically," New York Times (February 9, 1974), p. 37.

been used successfully to detect cervical and vaginal cancer. Light refractions of each cell from cervical smears are examined by a computer for comparison with known light patterns for malignant cells.[12]

INCENTIVES TO EARLY SCREENING

The National Cancer Institute (NCI) has awarded a contract to the Blue Cross Association to work toward developing financially attractive programs for early screening of cancer. The NCI hopes to encourage more outpatient clinic screening using allied health personnel to make these programs cost effective. Costs associated with late or end stage cancer can possibly be reduced through widespread early testing.[13] NCI reports that a growing number of cancers are now diagnosed when the tumor is still localized to site of origin, particularly for cancers of the breast, uterus, rectum, bladder, and prostate.[14]

Risk Factors—Theories

Definitions of risks associated with cancer could lead to more cost-effective cancer control programs, reduced mortality rates, and improved quality of life for patients with cancer.

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[12]"Laser Light for Cancer Detection," Science News, Vol. 108, No. 19 (November 8, 1975), p. 297.

[13]"Blues: Is Ca Screening Cost-Effective?" Medical World News, Vol. 17, No. 24 (November 1, 1976), p. 32.

[14]"NCI Reports Encouraging Upswing in Early Detection of Cancer," News and Features from NIH (May 25, 1975), pp. 6-7.

RISKS INHERENT IN THE HOST

Genetic and Family Diseases

The origins of cancer in children often can be traced to their parents. Congenital anomalies are particularly important: the mother of three children with Wilm's tumor and a fourth with a duplication of the left renal system was discovered to have congenital hemihypertrophy. This condition usually occurs in conjunction with Wilm's tumor or genitourinary disorders, or both. In this case the individual elements of the disorder were not concentrated in a single person but appeared in her offspring as well.[15]

Emphasis on obtaining detailed family histories will be of value in early identification of cancer. Particularly significant conditions include: cancer, paraneoplastic conditions, ectodermal dysplasias, immuno deficiencies, and congenital anomalies.[16]

Genetic tendencies toward cancer will continue to be one of the most complex research areas until greater knowledge of genetic processes and DNA coding is available. Familial risk of cancer has been clearly defined for several genetically transmitted cancer conditions: familial polyposis coli, Gardner syndrome, von Recklinghausen neurofibromatosis, hereditary endocrine adenomatosis types 1 and 2, multiple mucosal neuroma, retinoblastoma, veroderma pigmentosum, and more than 40 other cancers.[17] Most of these cancers

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[15] A. T. Meadows, J. L. Lichtenfeld, and C. E. Koop, "Wilm's Tumor in Three Children of a Woman with Congenital Hemihypertrophy," New England Journal of Medicine, Vol. 291, No. 1 (July 1974), pp. 23-24.

[16] J. M. Gerson, "Letter: Studies of Parents for Clues to the Origins of Cancer in Their Offspring," New England Journal of Medicine, Vol. 291, No. 11 (September 12, 1974), p. 583.

[17] H. T. Lynch, Cancer Genetics (Springfield, Ill.: Charles C. Thomas Publishers, 1976), p. 639.

are rare; some are lacking in clinical symptoms, making them nearly impossible to diagnose without detailed family studies.

Additional cancer risk from more common cancers also appears in individuals with a family history of cancer. In one study 9 percent of persons with one cancer in the family had cancer themselves; 16 percent of those with two cancers in the family had cancer; 27 percent with three or more cancers in the family had cancer. This familial effect has been found to be influenced by age, family size, carcinogenic exposures, and possibly racial and socioeconomic status.[18]

Immune System Deficiencies

The field of cancer immunology includes studies of:

1. Immunodeficiency in the etiology, pathogenesis, and history of cancer.
2. Immunosuppression by various cancer treatment approaches.
3. Tumor-associated antigens and tumor-specific immunity to these antigens.
4. Cancer immunodiagnosis.
5. Immunotherapy of cancer.[19]

Several immunologic tests have been developed in recent years that are helpful in managing cancer patients. Most are based on the presence of tumor-specific immune responses and antigens. Tests of general immunocompetence can identify patients with a poor prognosis so that further tests to look for recurrent or residual disease can be undertaken. The diffused

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[18] H. T. Lynch, et al., "Familial Risk and Cancer Control," Journal of the American Medical Association, Vol. 236, No. 6 (August 9, 1976), pp. 582-584.

[19] E. M. Hersh, G. M. Mavligit, and J. U. Gutterman, "Immunological Evaluation of Malignant Disease," Journal of the American Medical Association, Vol. 236, No. 15 (October 11, 1976), pp. 1739-1742.

presence of tumor antigens allows clinicians to estimate the extent of the disease quite accurately. One assay for carcinoembryonic antigen is now commercially available.[20]

Immune monitoring systems which are less efficient in the aged have been proposed as a mechanism for cancer; altered cells are not removed rapidly enough and begin tumor growth. This theory has received wide support, although a 1974 study found no spontaneous tumor increase in mice deprived of T-lymphocytes.[21]

Tests are under development to detect specific antigens which indicate the presence of a tumor at an early growth stage. These antigens have been found in tumors from colon, breast, and liver cancers in humans and animals. In the future it may be possible to use these antigens to screen normal populations for early hidden tumors.

Augmenting a patient's natural immunity to cancer has been attempted by several methods. Injecting lymphocytes (from an individual whose similar tumor regressed) into a cancer patient has not been very effective to date. Increasing the antigenicity of malignant cells is also under study. Some success has been reported with BCG, a tuberculosis vaccine, in stimulating the immune system to attack cancer cells and also when directly injected into tumors.

Transfer factor (TF), discovered more than 20 years ago, is an immunologic substance prepared from human lymphocytes. TF can be administered

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[20] Ibid.

[21] "Ageing and Cancer," The Lancet, No. 7951 (January 17, 1976), pp. 131-132.

repeatedly without causing antibody formation. All of the cell-mediated "memories" of the donor are transferred, and the recipient acquires sensitivity to the microbes and organisms on which the donor has reacted. TF has been successfully used to treat diseases ranging from warts to leprosy. At the University of California transfer factor has been used in treating patients with malignant malanoma, osteogenic sarcoma, and kidney cancer.[22] The substance will need to be synthesized and further researched before widespread application is possible. It will probably be a back-up treatment rather than principal therapy in the future to restore a patient's immunity and protect against recurrences after surgery.[23]

Jonathan W. Uhr has developed an immunoadsorbent machine to manipulate antibody levels in the blood. Specific antigens are stored on immunoadsorbent particles in a glass column. The patient's blood is driven through the column and returned to his body. Thus a cancer patient's blood might be cleansed of the antibodies protecting a malignant tumor. This procedure has not yet been clinically applied.

Immunochemotherapy of lung cancer has been reported to successfully control the disease for up to 39 months, and widespread clinical trials are expected to begin soon.[24] The therapy also may be effective in treating

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[22]J. Zanelli, "Transfer Factor: Science or Magic?" New Scientist, Vol. 63, No. 914 (September 12, 1974), pp. 646-648.

[23]D. N. Leff, "Trials for Transfer Factor," Medical World News, Vol. 17, No. 15 (July 12, 1976), pp. 59-62, 64-66, 70.

[24]"Purified Lung Cancer Antigen Proves Useful in Immunochemotherapy Trial," Journal of the American Medical Association, Vol. 236, No. 2 (July 12, 1976), pp. 119-121.

lung cancer patients who have no evidence of residual tumor after surgery.[25]

Recently one of the first immunology researchers stated that cancer immunotherapy has been misdirected for the past decade. Peter Alexander of the Chester Beatty Research Institute in England observed that no procedure against tumor-specific antigens has been proven clinically effective against cancer. He claims that researchers have failed to translate immunotherapy from mouse to man; in the latter patients usually die of distant metastases rather than operable tumors. "All we did," he says, "was substitute a complex immunologic procedure for a simple surgical excision."[26] Future immunotherapy is more likely to be directed against non-specific immunogens and used adjunctively with more traditional methods.

PERSONALITY

A 28-year study by a Johns Hopkins researcher has uncovered a surprising link between personality type and cancer incidence. Cancer victims tended to be less anxious and depressed, and were generally placid, gentle, and non-aggressive. They were, however, not close to their parents, and this trait has been confirmed in other retrospective studies that cancer-prone personalities are alienated in childhood could link up with the theory of immunity: stresses and conflicts from childhood may render the organism incapable of fighting off malignancies.

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[25] International Medical News Service, "Immunotherapy Seen 'Promising Modality' for Some Lung Cancers," Internal Medicine News, Vol. 9, No. 20 (October 15, 1976), pp. 34-35.

[26] "It's Back to the Drawing Boards for Cancer Immunotherapy," Medical World News, Vol. 17, No. 24 (November 1, 1976), pp. 45, 47.

In comparing cigarette smokers, a British research team found that lung cancer patients appeared to be unable to release their emotions through usual outlets. Psychiatrists at the University of Rochester found that a life history of trial combined with a sense of hopelessness may predispose some to cancer.[27] At the Third International Symposium on Detection and Prevention of Cancer held in April 1976, researchers from England and the United States reported similar findings: likely cancer candidates are women who have always suppressed or always vented their anger.[28]

These findings suggest that cancer-prone personality types may be identifiable early in life by means of a widely administered psychological test. High risk individuals might then be more closely monitored for cancer. Until this theory is better established and more widely accepted, however, such tests are not likely to be productive.

HORMONE CHANGES

One school of thought in cancer holds that age-related changes in the hypothalmus lead to alterations of the hormonal environment which in turn leads to cancer. The association between breast cancer and total fat consumption is well documented;[29] epidemiological studies also correlate fat consumption with cancers of the uterus, ovary, and testis. These results

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[27] J. I. Rodale, Happy People Rarely Get Cancer (Emmaus, Penn.: Rodale Press, Inc., 1970).

[28] "Cancer Linked to Personality Traits," Medical World News, Vol. 17. No. 12 (May 31, 1976), pp. 17-18.

[29] K. K. Carroll, E. B. Gammal, and E. R. Plunkett, "Dietary Fat and Mammary Cancer," Canadian Medical Association Journal, Vol. 98 (1968), pp. 590-594.

suggest a connection between dietary fat and hormonal factors. One study using rats found that mammary tumor cell growth is stimulated when the ratio of prolactin to estrogen is high. The experiment showed that when serum prolactin levels were depressed, the effects of different dietary fat levels on mammary tumor development were no longer evident. Thus the tumor-enhancing effect of high fat intake appears to be mediated by prolactin.[30]

Clinicians have observed that a substantial portion (5 to 10 percent) of persons who develop cancer at one time in their lives will have a recurrence later on, sometimes in another organ or tissue.[31] This would suggest that cancer is an immunosuppressive problem, an hereditary predisposition, or continuing exposure to an environmental carcinogen. However, certain patterns of cancer recurrence may not fit these patterns. The fact that women who develop breast cancer are at greater risk of developing ovarian cancer appears to support the theory of hormonal mediation mentioned above.

ACCUMULATION OF CELLULAR EVENTS

Increased incidence of cancer among the elderly has been theorized to result from a steady accumulation of many cellular events required for cancer formation rather than any inherent effect of old age. Irreversible changes building in tissue cells take place gradually over a period of years. Data on lung cancer incidence and age of first smoking appear to support this

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[30] H. Chann, et al., "The Butterfat Absorption Test in Adults," Digestive Diseases, Vol. 20, No. 10 (October 1975), pp. 914-922.

[31] J. E. Brody, "Multiple Cancers Termed on Increase," New York Times (October 10, 1976), p. 25.

theory: duration of exposure to the cancer causing agent appears to be more important than actual age in influencing cancer morbidity.[32]

Environmental Risks

The Subcommittee on Environmental Carcinogenesis of the National Cancer Institute estimates that the NCI spends about 10 percent of its total budget on the field of environmental carcinogenesis.[33] Public awareness of environmental carcinogens, combined with growing cancer prevalence, probably will lead to an increase in research and testing in this field perhaps at the expense of the more "glamorous" fields of immunology and virology.

POLLUTANTS AND OCCUPATIONAL EXPOSURE

Occupational exposure to carcinogenic substances such as asbestos, chromates, arsenicals, and nickel are documented almost daily. Five to fifteen percent of all current cancer deaths in males are estimated to be occupational in origin, including:

- Lung cancer and pleural mesotheliomas in insulation workers, construction workers, and others exposed to asbestos.
- Bladder cancer in aniline dye and rubber industry workers.
- Lung cancer in uranium miners, coke oven workers, and those exposed to bischloromethyl ether.
- Skin cancer in cutting and shale oil workers.

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[32]"Ageing and Cancer," The Lancet, No. 7951 (January 17, 1976), pp. 131-132.

[33]Subcommittee on Environmental Carcinogenesis, "Report Presented at the National Cancer Advisory Board Meeting, March 17-18, 1975," monograph.

- Nasal sinus cancer in woodworkers.
- Cancer of the pancreas and lymphomas in organic chemists.
- Angiosarcoma in workers manufacturing and fabricating polyvinyl chloride.

Commonplace environmental pollutants, while safe in single exposures, can increase risks of cancer when exposures are repeated, according to a recent Library of Congress study. The report adds that only a small portion of the damage can be recognized with current detection abilities, that expensive and lengthy testing methods are not adequate to detect many polluting agents. Environmental problems may account for as much as 70 to 90 percent of cancer causes, the Library of Congress study concludes, although about 80 percent of the pollutants which may lead to cancer are naturally occurring.

Controlling environmental carcinogens poses enormous problems and requires the consideration of many interrelated variables: the length of time of exposure, the level of exposure, the population involved, the level of potency. Social and political variables also are important: cigarettes and alcohol are believed by some to be responsible for about half of all cancers in the United States. Guidelines for toxic substance testing will be extremely difficult to determine. Within certain occupational groups incidence of cancer is astonishingly high. An estimated 50 percent of long-term asbestos-insulation workers die of cancer, and approximately one-third of all early deaths in uranium miners is due to lung cancer.[34]

A great number of test systems to detect possible carcinogens are under study today. The so-called Ames test has limited application but is believed

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[34] S. S. Epstein, "The Political and Economic Basis of Cancer," Technology Review, Vol. 78, No. 8 (July-August 1976), pp. 35-43.

to be valid, reliable, and simple. The test takes only three days to complete at a cost of about $200. The test does not measure carcinogenocity directly but measures the mutagenic capabilities of test substances on a specific bacterium. It measures not only whether a substance is mutagenic but to what degree as well. This dose-responsive information—quite difficult to discern from animal trials—is of critical importance in evaluating environmental carcinogens. More than 100 research laboratories around the world have experimented with Ames test or a variation, and over 50 industrial companies have requested samples. Such tests cannot define carcinogens —only large-scale animal testing indicates carcinogenicity—but probably will be most helpful in prescreening environmental chemicals before conducting more expensive and time-consuming animal trials.[35] In animal testing very high exposure levels are usually required to obtain results quickly. From this point "translation of the data to predict the hazard of low level exposure is presumptuous guesswork at best," according to Perry J. Gehring, director of the Toxicology Research Laboratory at Dow Chemical.[36]

The Toxic Substances Control Bill, S.3149, was signed into law in October 1976. Beginning January 1, 1977, all chemical manufacturers have been subject to its provisions. The passage of this legislation ended six years of debate between industry and environmental groups. Chemical manufacturers no longer may market new chemicals without first notifying the U.S. Environmental Protection Agency (EPA). If EPA determines that it does not have

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[35] R. Lewin, "Cancer Hazards in the Environment," New Scientist, Vol. 69, No. 984 (January 22, 1976), pp. 168-169.

[36] "Needed in Cancer Controversy: Facts," Chemical Week, Vol. 118, No. 11 (March 17, 1976), pp. 13-14.

enough information on the safety of the chemical, the manufacturer is notified that the agency will prohibit production and marketing. An interagency advisory committee will develop a priority list of already available chemicals which should be tested. EPA will compile an inventory list of existing chemicals not subject to premarketing notifications. Growing public awareness of the potential environmental nature of most cancers and a series of disturbing well publicized occurrences (contamination of fish in the Hudson River, polychlorinated biphenyls in the Great Lakes) have been credited with aiding passage of this legislation, generally regarded by all lobbies as a genuine compromise. Implementation of the bill will be cumbersome, the staffing is likely to be inadequate, and the financing of the efforts is considered by many experts to be insufficient--$10 to $16 million over the next three years. This is in contrast to the $40 million annually spent by EPA to regulate pesticides. One industry official estimates that EPA must spend $200 million annually to implement the legislation.[37]

RADIATION

Cancer risks associated with the operation of nuclear power plants are frequently mentioned by critics of atomic power facilities, but the issue also is clouded by political and economic arguments raised by both sides of the debate. One radiation physicist estimates that a single pound of reactor-grade plutonium released into the atmosphere could cause over 300 million cases of lung cancer. Gofman calculates that lung cancer deaths will increase

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[37]"Learning To Live with Toxic Controls," Chemical Week, Vol. 119, No. 16 (October 20, 1976), pp. 43-44.

from 80,000 to 500,000 annually even if future breeder reactors are operated at nearly absolute containment efficiency.[38] Some observers believe Gofman's estimates are radically alarmist. A Battelle Laboratories report projects from animal studies that current maximum permissible lung doses for workers exposed to plutonium particles are too low. One scientist adds, "Research never has shown a level at which plutonium is not dangerous."[39] Yet another 27-year study of plutonium workers in New Mexico found no medical indications could be traced directly to internally depcsited plutonium.[40]

X-rays and similar forms of radiation in high doses have been conclusively linked to leukemia and other cancers. Survivors of the Hiroshima and Nagasaki atomic blasts have a higher incidence of leukemia as well as cancers of the breast, bowel, and brain. Risks from conventional diagnostic X-rays are not as well established. Some researchers argue that one rad of radiation ages the cells it strikes by at least one year. One physicist attributes 7500 annual cancer deaths to current annual radiation exposure from medical sources.[41]

ALCOHOL AND COFFEE

A study by the National Institute on Alcohol Abuse and Alcoholism indicates that heavy drinking increases risk of developing cancer of the oral

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[38] J. W. Gofman, "The Plutonium Controversy," Journal of the American Medical Association, Vol. 236, No. 3 (July 19, 1976), pp. 284-286.

[39] "M.D.'s Join the Nuclear Safety Debate," Medical World News, Vol. 17, No. 2 (January 26, 1976), pp. 57-58.

[40] Ibid.

[41] "Millions of X-Rays Found Unneeded and Radiation Is Often Excessive," New York Times (January 30, 1976), p. 10.

cavity, esophagus, and larynx. While these are some of the same cancers associated with cigarette smoking, government officials are reluctant to label alcohol as a carcinogen. Cancer of the tongue and the hypopharynx also are apparently related to heavy use of alcohol. This link becomes more important in an era of growing alcohol abuse among younger Americans. Also, for persons who both smoke and drink, the risk of cancer rises disproportionately.

Coffee and caffeine have been implicated in a number of cancer studies, but no real evidence of health hazard has yet been determined. Caffeine is both teratogenic and mutagenic, although many of the implicating laboratory tests conducted years ago would be considered inadequate by today's standards. One theory holds that caffeine acts as a cocarcinogen by fostering the formation of nitrosamines from secondary amines and nitrites in the stomach. On the other hand, there is evidence that caffeine has anticarcinogenic effects in animals exposed to known carcinogens. Also, caffeine is metabolized quickly and efficiently in man. Suspicion of risk associated with coffee includes several cancers: bladder, renal, and renal pelvic cancers.[42]

TOBACCO

Smokers are the least debatable, best documented high risk group for one of the deadliest cancers, cancer of the lung.

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[42]"Caffeine, Coffee, and Cancer," British Medical Journal, No. 6017 (May 1, 1976), pp. 1031-1032.

DIET AND NUTRITION

Nutrition has been found to be associated with cancer in two ways: first, certain dietary habits have been positively correlated with cancer incidence and second, successful therapy of cancer often depends on a patient's nutritional condition.

Dietary habits have been linked with more than half of all cancers in men and at least one-third of all female cancers. Epidemiological studies of migrant populations, Mormons, Seventh Day Adventists, and specific ethnic groups have established definite relationships between eating habits, food preferences, and cancer. Gastric cancer is associated with pickled vegetables, dried salt fish, and starch (a common staple among the poor). Gastric cancer is negatively correlated with raw vegetables and milk. These foods are frequently eaten in Japanese homes which may account for their lower incidence of gastric cancer. (See Figure 1.) Colon cancer correlates highly with fat consumption and meat. Also, breast cancer relates to fats, particularly saturated fats. Caloric restriction generally inhibits tumor formation: spontaneous neoplasms of the breast can be reduced with caloric reductions.[43]

Most researchers concur that environmental carcinogens or foods containing carcinogens are not as important as nutritional deficiencies and/or excess in cancer development. Heavy users of saccharin and cyclamates, for instance, are not more likely to get colon, stomach, or breast cancers than other persons; rather, poor or unbalanced nutrition alters the metabolic processes that later permit certain forms of cancer to appear. Some researchers

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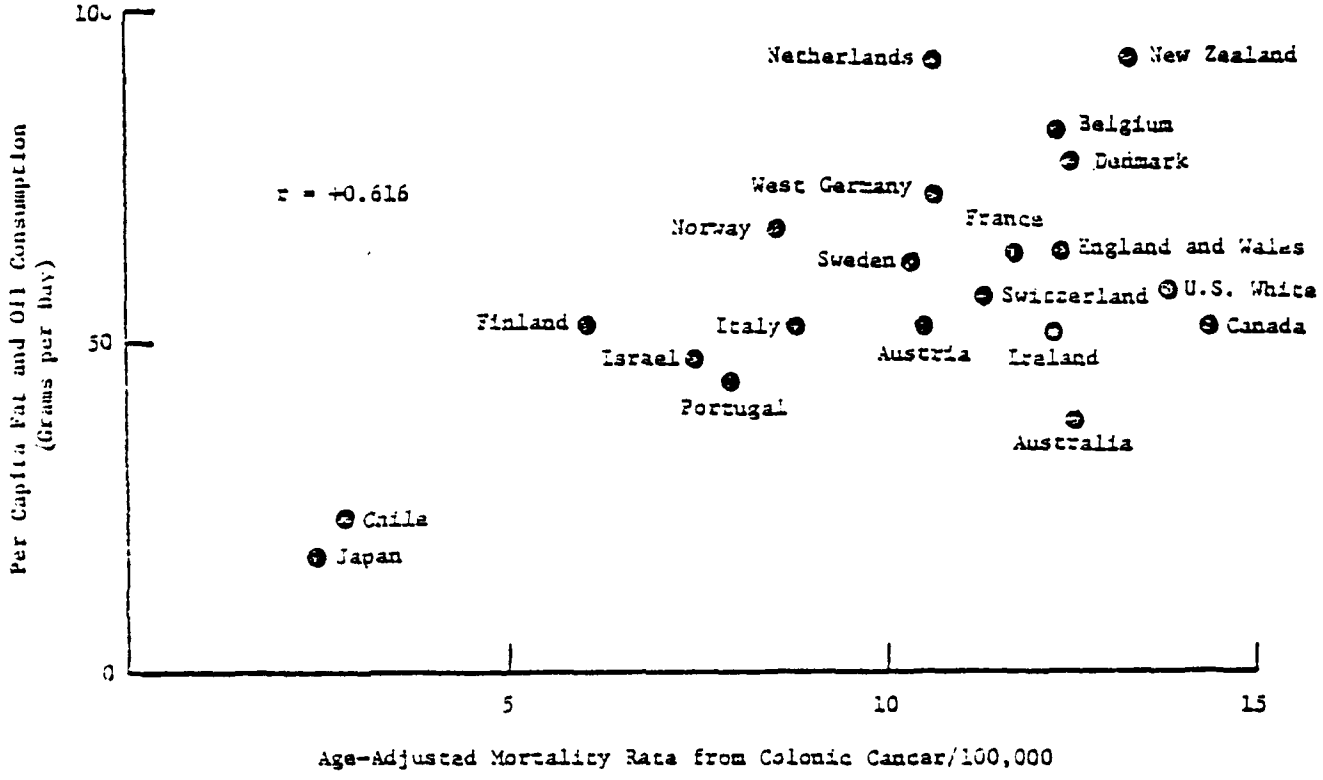
[43] G. B. Gori, "Statement Before the Select Committee on Nutrition and Human Needs, United States Senate," July 28, 1976.



SOURCE: Ernst L. Wynder, "The Epidemiology of Large Bowel Cancer," Cancer Research, Vol. 35, No. 11, Part 2 (November 1975), p. 3390.

Figure 1. Bowel cancer mortality and dietary fat and oil consumption

believe that the continual low level insult to the body of poor diet weakens the natural defenses of an organism and leads to the appearance of some cancers.[44]

Vitamin A, alone or in food, appears to inhibit cancer of the stomach and cervix caused by carcinogenic hydrocarbon compounds. Lack of vitamin A apparently contributes to cancer of the salivary glands.

Nutrients or diet probably relate to cancer through any one or any combination of the abilities to:

1. Act as carriers of a procarcinogen or carcinogen (e.g., nitrates in meat).

2. Alter intestinal flora that act on procarcinogens to convert them to carcinogens.

3. Increase the level of cocarcinogens such as certain fatty acids and sterols.

4. Alter tissue structure so that it is more susceptible to the action or penetration of the carcinogen as well as the cocarcinogen (e.g., diets that increase the concentration of sterols in the intestinal lumen and that have been implicated in enhancing chemical carcinogenesis).

5. Influence the host-defense system or one of its components, rendering the animal and/or organ more susceptible to the chemical carcinogen.[45]

High fat diets are suspected of causing colon cancer because the fat may affect both the composition of intestinal microflora and their metabolic activity, in addition to increasing the levels of certain steroids

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[44]"Some Tests More Promising Than Predictive," Medical World News, Vol. 17, No. 24 (November 1, 1976), p. 32.

[45]"Blues: Is Ca Screening Cost-Effective?" Medical World News, Vol. 17, No. 24 (November 1, 1976), p. 32.

which may act as tumor promoters for the colon.[46] While researchers acknowledge that dietary factors are strongly implicated in the etiology of colon cancer and the evidence against dietary fat is substantial, it is by no means conclusive. One epidemiological study found a stronger correlation between colon cancer and meat consumption than between colon cancer and total fat consumption.[47]

The role of dietary fiber in the American diet has been the subject of considerable emphasis in the lay and medical press, and some of the literature would lead one to think that all western man need do is restore fiber to his diet and he will be saved from the heart and circulatory diseases. Studies that compared bowel movement frequency and fecal weight between primitive people with a high fiber diet and those consuming a typical western diet would suggest that dietary fiber may help prevent many of the so-called "civilized" diseases that have characterized the developed western cultures of the twentieth century. These epidemiologic studies have initiated a great deal of scientific interest, but the complex physiological and biochemical explanations have not surfaced.

Transit time of food moving from mouth to anus may be an important factor in colon cancer, and dietary fiber does speed up transit time. Some researchers believe viruses are responsible for colon cancer; others think the carcinogen could be a by-product of the action of intestinal bacteria on food, digestive, or excretory material. Still others think colon cancer

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[46] B. S. Reddy, et al., "Animal Models for the Study of Dietary Factors and Cancer of the Large Bowel," Cancer Research, Vol. 35, No. 11, Part 2 (November 1975), pp. 3403-3406.

[47] B. K. Armstrong, et al., "Commality Consumption and Ischemic Heart Disease Mortality, with Special Reference to Dietary Practices," Journal of Chronic Disease, Vol. 28, No. 9 (October 1975), pp. 455-469.

may be caused by carcinogenic chemicals in foods. But regardless of the agent, the consensus is that the longer it takes for foods to travel through the alimentary tract, the longer the colon is exposed to the harmful agent. This complex problem offers no easy solutions because researchers are only beginning to understand the effects of different fats and fibers.

Cancer patients often are malnourished from anorexia and are thus less able to withstand therapy from radiation, surgery, or drugs. Nutrition therapy focuses on restoring taste patterns. Other research is aimed at the differences in nutritional requirements between malignant and normal cells; scientists hope to adjust available nutrients to feed host cells and starve cancer cells.[48]

VIRUSES

A substantial share of cancer research has centered around the field of virology. Clinical observations do not seem to support the viral concept: cancer is not contagious at the home, hospital, or in laboratory dissection, and cancer can be induced in experimental animals by chemicals or radiation. Yet a few animal tumors and leukemias have been confirmed as caused by transmissible viruses.[49] Cancers linked to common virus include cancer of the cervix, cancer of the upper respiratory tract, Hodgkin's disease, Burkitt's lymphoma, and possibly leukemia and breast cancer. Most

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[48] G. B. Gori, "Statement Before the Select Committee on Nutrition and Human Needs, United States Senate," July 28, 1976 (Bethesda, Md.: National Cancer Institute, 1976).

[49] L. Gross, "The Role of Viruses in the Etiology of Cancer and Leukemia," Journal of the American Medical Association, Vol. 230, No. 7 (November 18, 1974), pp. 1029-1032.

researchers theorize that the original viral infection occurs early in life and the virus becomes incorporated in the genetic makeup of certain body cells. Years later these transformed cells divide and multiply to produce many other cancer cells. Genetic predisposition, the body's immune system, the presence of other viruses, and exposure to noxious chemicals are thought to influence this rather rare transformation of cells.[50] In most persons who are infected by viruses, no cancer occurs so that viral cancer is not an infectious disease in a traditional sense.

In the early 1970's cancer viruses found in human tissues caused considerable excitement in the scientific community. In 1974 Michigan Cancer Foundation scientists reported isolation of a human virus implicated in breast cancer. Early in 1975 a virus associated with human leukemia was discovered by National Cancer Institute researchers.[51] Two primate tumor viruses were identified in 1972, and the human cancer virus has specific similarities to them. Even if the virus is an exogenous agent, data indicate that leukemia and other cancers are not contagious in the usual sense; genetic factors and environmental influences coincide with the virus to produce the cancer.[52]

A massive four-year population study in Africa supports the viral theory of cancer. From blood tests, virus antibodies were screened in persons

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[50]"Data Build Up on Cancer-Causing Viruses," Chemical and Engineering News, Vol. 53, No. 14 (April 7, 1975), pp. 18-19.

[51]R. E. Gallagher and R. C. Gallo, "Type C RNA Tumor Virus Isolated from Cultured Human Acute Myelogenous Leukemia Cells," Science, Vol. 187, No. 4174 (January 31, 1975), pp. 350-353.

[52]T. H. Maugh, "Leukemia: A Second Human Tumor Virus," Science, Vol. 187, No. 4174 (January 31, 1975), pp. 335-336.

without cancer, and those with particularly high levels were monitored. All of the subjects, Ugandian children, had Epstein-Barr virus in their bloodstreams, indicating that the virus is prevalent in Uganda. The children who subsequently developed Burkitt's lymphoma had levels of EB virus two times higher than other children.[53]

Recent experiments suggest that Gallo virus described above is a mixture of viruses identical to the two earlier ape viruses. The herpes-type DNA virus—EB in the above study—remains the only definite human cancer virus. EB is very common throughout the world but only appears to be harmless except for Burkitt's lymphoma. Similar viruses cause cancer in frogs and chickens and the very common herpes simplex virus may be related to cervical cancer. National Cancer Institute researchers found that herpes simplex virus can activate latent tumor viruses but these latent viruses can be activated by many DNA-damaging treatments, so it is uncertain that herpes viruses are the cause.[54]

STRESS

Microbiologists at the Pacific Northwest Research Foundation found that chronic stress significantly affects the latent period of development of mouse mammary cancer. Apparently, stress causes the mouse's pituitary gland to activate the adrenal gland through very high plasma levels of corticosterone. Within a short time white blood cell count is halved and the thymus begins to

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[53] J. Arehart-Treichel, "Virus-Cancer Crosspoint," Science News, Vol. 108, No. 19 (November 8, 1975), pp. 298-299.

[54] "Is This How Herpes Viruses Cause Cancer?" New Scientist, Vol. 70, No. 999 (May 6, 1976), p. 290.

become involuted. If the stress is removed, the thymus returns to normal within two weeks.[55]

A Swiss researcher found persons living within 50 yards of a busy state highway are more likely to die of cancer than others living outside that range. Highway residents also are more subject to other physiologic and psychologic disturbances such as headaches, sleep disorders, fatigue, depression, anxiety, and digestive problems.

Treatment

RADIATION

Since supervoltage equipment was introduced to clinical practice over 25 years ago, radiation therapy has been very prevalent in cancer treatment. Currently about 50 percent of cancer patients receive radiation therapy at some time, often as a principal treatment method. Early seminoma of the testis, Hodgkin's disease, and larynx and cervix patients have obtained 90 percent survival rates as a result of radiation. Prostatic cancer and soft-tissue sarcomas, once believed incurable by irradiation, also have benefited from radiation. When radiation is combined with chemotherapy, prospects for survival are greatly enhanced for patients with Wilm's tumor and Ewing's sarcoma. Radiation also is a useful adjunct to surgical treatment for the control of rectal cancer.[56]

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[55] V. Riley, "Mouse Mammary Tumors: Alteration of Incidence As Apparent Function of Stress," Science, Vol. 189, No. 4201 (August 8, 1975), pp. 465-467.

[56] W. D. Bloomer and S. Hellman, "Normal Tissue Responses to Radiation Therapy," The New England Journal of Medicine, Vol. 293, No. 2 (July 10, 1975), pp. 80-83.

DRUGS

Anticancer chemotherapy is one of the fastest growing therapeutic classes. Drug treatment has become more specific in recent years and may well supplant traditional treatments for some cancers. Initially, researchers sought a "magic bullet" drug effective for all forms of cancer. Recent knowledge suggests this goal to be inappropriate, and cancer chemotherapy has become more complex than ever before. Through trial and error, a number of promising leads have developed, particularly in the use of multidrug combinations.

The use of several drugs simultaneously (or in closely coordinated sequence) has led to dramatic improvements in childhood leukemia and adult lymphomas. Tests now are underway to develop similar "combos" to treat solid tumors, the form of cancer responsible for most cancer deaths. One researcher at the National Cancer Institute emphasizes the need for this research, "Surgery and radiation therapy have reached a plateau in their ability to cure solid tumors." Surgeons and clinicians have been unenthusiastic about chemotherapy except for rare cancers because of the significant side effects and a lack of proof of their effectiveness. Another important drawback in the use of anticancer drugs has been their toxicity to normal cells. Combination chemotherapy involves the selection of drugs with different mechanisms of action and different toxicities. When each drug is given in full dose the antitumor properties work additively and the toxicities to normal cells do not. This concept was applied to treat Hodgkin's disease with a combination of nitrogen mustard, vincristine, procarbazine, and prednisone (known as MOPP). The number of patients who went into complete remission under this program increased 400 percent. This form of chemotherapy

can be extremely complex, involving 10 or more drugs in various combinations with radiation and several cycles throughout treatment. Sloan-Kettering researchers have used a combination of four drugs in conjunction with other therapy to treat neuroblastoma, a usually fatal childhood nerve cancer. Testicular cancer, the fourth most common cause of cancer mortality in men aged 15 to 34, also may be treated in the future with a combination of drugs. Quite recently the National Cancer Institute reported intensive chemotherapy and radiation tripled the remission rate in a small group of patients with undifferentiated lung cancer ("oat cell cancer"). This form of lung cancer, affecting 15,000 Americans each year, has a survival rate of virtually zero. The combination used included bleomycin, doxurubicin, cyclophosphamide, and vincristine.

Experiments in Italy's National Tumor Institute suggest a combination of three drugs given after surgery to women with advanced breast cancer had dramatically lowered the usual rate of early cancer recurrence. The mortality rate for breast cancer--approximately 33,000 annually--has not improved significantly in the past five years, and these and other studies offer some hope for the future of breast cancer victims.

Of importance equal to the development of new anticancer drugs, the means of targeting these agents to reach only cancerous cells soon may be available. Swedish researchers have linked nitrogen mustard to an estrogen derivative so that the anticancer agent can be more directly delivered to prostate tumors. Other research combines cancer drugs with nutrients preferred by malignant cells.

Immunotherapy researchers are testing a number of products for their ability to fight tumors. Some of the agents under study include BCG

(bacillus Calmette-Guérin), a tuberculosis vaccine; DNCB (dinitrochlorobenzene), a sensitizing agent; levamisole, a deworming agent. Immunotherapy appears to be most appropriate today when used adjunctively with surgery or chemotherapy to prevent cancer recurrence of metastasisation following removal of the primary tumor. A recent study reports dramatically improved survival rates for Stage I lung cancer patients receiving BCG through intrapleural injections after pneumonectomy or lobectomy.

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