Ad Hoc 2/24/69

New Research Sparks Debate On

Researchers Say Smoking Causes *Aortic* Atherosclerosis

Recent research suggesting cigarette smoking causes aortic atherosclerosis has added new sparks to the hot debate over smoking and death from heart disease.

Results of the research project were reported by investigators at

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Investigators from Roswell Park Memorial Institute and the State University of New York at Buffalo have completed a study which suggests there is a causal relationship between smoking and *aortic* atherosclerosis.

While the investigators admit that there may not be an exact 1:1 relationship between aortic and coronary atherosclerosis, they point out the "similarity in findings between this work and identical studies of coronary arteries that have been published recently."

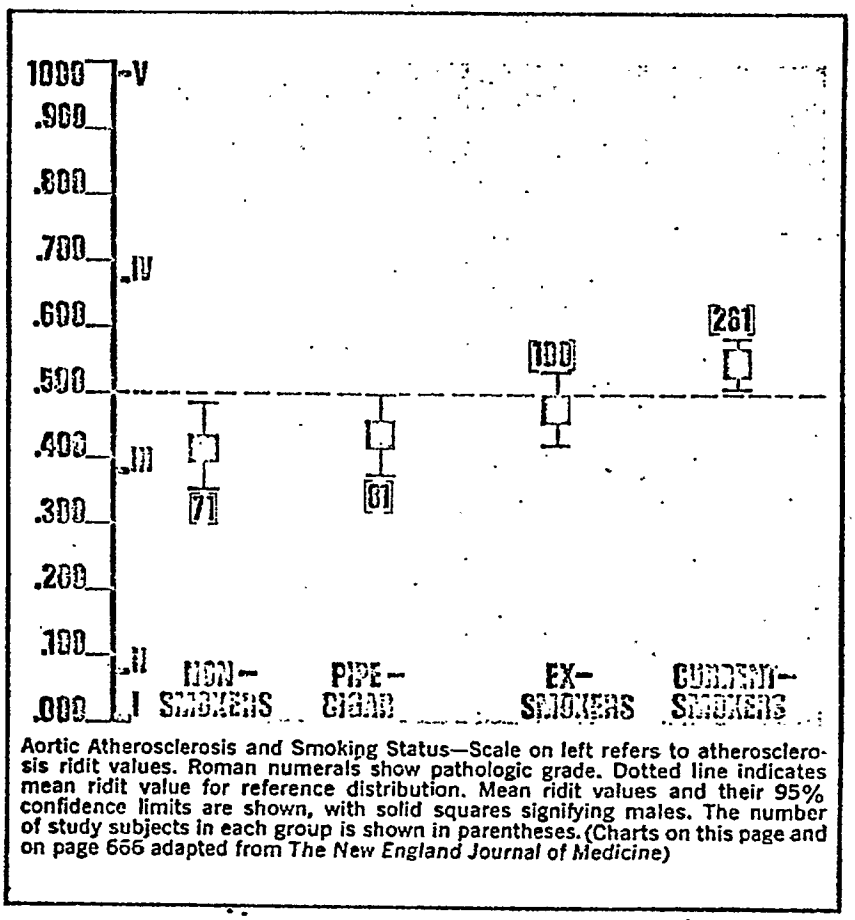
In the study of 1,019 patients admitted to Roswell Park, the investigators found a "graded and statistically significant increase in the severity of aortic atherosclerosis with increased use of cigarettes."

The most striking association in the study was, as expected, the one between age and aortic atherosclerosis. No such association was observed between aortic atherosclerosis and cigar-smoking, pipe-smoking, or alcohol consumption.

For the study, all patients admitted to Roswell Park during 1956 to 1964 were questioned about lifetime use of tobacco and alcohol. During the follow-up period (to 1964), 1,019 of these patients died, and autopsies were performed on all. At the time of the postmortem examination, each aorta was excised, preserved, and graded as to extent and severity of atherosclerosis in each artery. Cross-checking of responses to the standardized questionnaires and re-examination of a subsample of aortas confirmed the reproducibility of the data-gathering methods.

The investigators used a new statistical technique termed "ridit analysis" to summarize information for groups of individuals in relation to a given variable. In this way, they were able to obtain average values reflecting the clinical determination of the severity of aortic atherosclerosis for all individuals in groups arranged by age, sex, and degree of cigarette or alcohol consumption.

They compared these values to the mean atherosclerosis ridit for the reference group of non-smoking women 45 to 69 years of age. The mean ridit for any reference group is .500.



Aortic Atherosclerosis and Smoking Status—Scale on left refers to atherosclerosis ridit values. Roman numerals show pathologic grade. Dotted line indicates mean ridit value for reference distribution. Mean ridit values and their 95% confidence limits are shown, with solid squares signifying males. The number of study subjects in each group is shown in parentheses. (Charts on this page and on page 666 adapted from *The New England Journal of Medicine*)

Patterns Observed

The average ridit for the 14 nonsmoking, non-drinking male subjects aged 50 to 69 was .455. It was .500 for the 11 users of alcohol alone, and .675 for the 29 users of cigarettes alone. The 174 users of both alcohol and cigarettes had a mean ridit of .683. A similar pattern was observed in other age groups.

Pooled data for all males under 70 years of age produced the following ridit values: .371 for nonsmoking and non-drinking subjects, .453 for alcohol users, .602 for smok-

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Smoking And Heart Disease Deaths

. . . But How Does That Relate To Coronary Atherosclerosis?

Roswell Park Memorial Institute. But, when questioned, other investigators have voiced disagreement with some of the conclusions of the Roswell Park team. MEDICAL NEWS reports on the Buffalo research and the debate.

ers, and .613 for users of both.

The use of alcohol alone appeared to be associated with a slight increase in ridit value. However, they said, the statistically insignificant differences between the group using cigarettes alone and the group using both cigarettes and alcohol indicate that alcohol consumption had little effect upon the severity of atherosclerosis.

They thought the reason for the lack of association might be due to under-representation of study subjects with extremely high and prolonged levels of alcohol intake.

Degree Of Smoking

When the degree of smoking was considered, the investigators found a statistically significant increase in the atherosclerosis ridit (or severity of aortic atherosclerosis) as the amount of cigarettes (up to one package a day) and the years of smoking increased.

Ex-smokers had ridit values about half-way between those of smokers and non-smokers.

The team of investigators was headed by David L. Sackett, MD, now chairman of the Department of Clinical Epidemiology and Biostatistics of the new Faculty of Medicine at McMaster University in Ontario. Working with Dr. Sackett in Buffalo, where he was an associate professor of medicine and preventive medicine and director of the clinical epidemiology unit, were: John W. Pickren, MD, chairman of the pathology department at Roswell Park; Irwin D. J. Bross, PhD, chairman of the Department of Biostatistics and acting director of the epidemiology department; and Robert W. Gibson, doctoral candidate in the epidemiology department. Dr. Bross developed the technique of ridit analysis.

The real question is: "Can we assume that what's going on in the aorta is also going on in the coronary arteries?"

That is the way William Kannel, MD, put it when asked to comment on the study. Dr. Kannel is director of the Framingham (Mass) Heart Disease Epidemiology Study.

"While the Roswell Park study may relate to the atherosclerotic process in general," Dr. Kannel said, "the relationship between this process and coronary artery disease is not perfect, and coronary artery disease is our major concern." The general tendency to lay down fatty deposits depends to some extent on local factors, he explained, and the local factors in the aorta are certainly different from those found in the coronary arteries.

In addition to similarity in findings between studies on coronary and aortic atherosclerosis, the investigators believe other evidence suggests a correlation between the degree of atherosclerosis in the aorta and in other vascular sites. Such a correlation is demonstrated, they said, by the fact that patients demonstrating radiographic aortic calcification have a significantly increased risk of stroke.

According to Dr. Kannel, the results of most studies do not support the premise that smoking has a direct and long-term influence on the atherosclerotic process—such as that observed by Dr. Sackett. Instead, Dr. Kannel believes that smoking may trigger the lethal event in individuals with occult evidence of coronary artery disease, but it does not accelerate the atherosclerotic process itself.

"Moreover," Dr. Kannel said, "studies have shown that the effects of cigarette smoking with regard to atherosclerosis are transient, noncumulative, and reversible." For example, he said, in those who stop smoking, the risk of mortality from coronary artery disease falls back toward that of non-smokers.

According to Dr. Sackett's group, smoking may have both short-term effects and long-term effects on the arterial wall. This is suggested, they said, by the finding that severity of aortic atherosclerosis is related to duration of smoking and that ex-smokers continue to show more aortic atherosclerosis than nonsmokers.

Carl C. Seltzer, PhD, noted that Dr. Sackett's study included only cancer patients. "Obviously, people admitted to a specialized hospital such as Roswell Park are not representative of the general population."

Dr. Seltzer, senior research associate in biological anthropology at Harvard University School of Public Health, recently published an article questioning the validity of using epidemiologic studies to show a causal relationship between cigarette smoking and coronary heart disease (*JAMA* 203:127 [Jan 15] 1968).

In commenting on the work of the Buffalo group, Dr. Seltzer said that other studies of unselected populations have shown no causal relationship. For example, postmortem examinations of series of accident victims reveal no correlation between smoking and atherosclerosis.

Neither was such a relationship observed in autopsies performed on 85 subjects from the Framingham study. Dr. Kannel said: "There was no relation between smoking and uncomplicated coronary atherosclerosis in those not dying of coronary heart disease."

According to Dr. Sackett, the cancer hospital was purposely chosen for the study because admissions were not directly influenced by the

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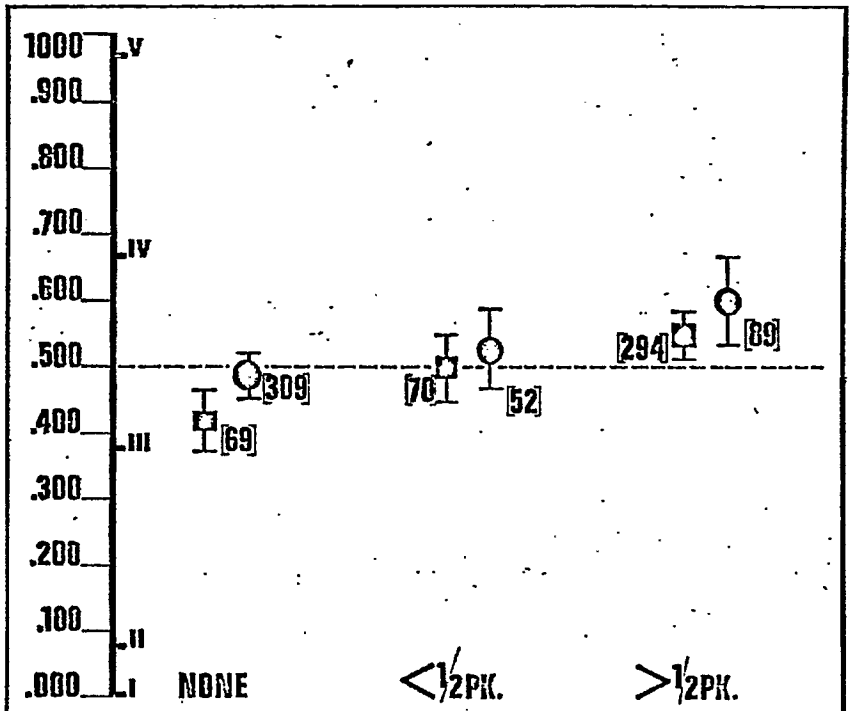

Aortic Atherosclerosis and Intensity of Smoking—Scale on left refers to atherosclerosis ridit values. Roman numerals show pathologic grade. Dotted line indicates mean ridit value for reference distribution. Mean ridit values and their 95% confidence limits are shown, with solid squares signifying males and solid circles females. The number of study subjects in each group is shown in parentheses.

Smoking And Heart Disease

(Continued from previous page)
presence or absence of aortic atherosclerosis, nor by the consumption of cigarettes or alcohol.

Dr. Sackett also said earlier work has shown that cancer and aortic atherosclerosis are not associated. Of course, the possibility of overrepresentation of persons with both disorders remains when using a hospital population. Patients with more than one disease are more likely to seek and receive hospitalization because of the greater disability and discomfort which probably exists. This could lead to the false conclusion that the two disorders are causally related, the New York group said.

Another problem with retrospective studies of this type is the faulty collection of historical data. This potential bias has been avoided, the investigators believe, by including only patients admitted during a period when all underwent standardized interviews.

Dr. Seltzer also criticized the study as being strongly under-represented by non-smokers. In response, Dr. Sackett pointed out that there were 56 non-smokers in the series of 433 males (not including the 81 pipe and cigar users and the 39 with incomplete responses). Of the 450 females (excluding 16 with incomplete responses), 311 did not smoke.

Dr. Seltzer commented: "I still feel quite strongly that there is no evidence to suggest a causal relationship between smoking and coronary heart disease."

Dr. Kannel said: "No one can dispute the statistical association between mortality from coronary heart disease and smoking, nor the fact that the intensity of smoking is related to the risk of mortality from this disease. However, at the present time, we don't know if that relationship is causal."

In spite of the finding that the risk of mortality from coronary heart disease decreases rapidly in ex-smokers, Dr. Sackett believes that the study confirms the work of other investigators who have concluded that cigarette smoking is associated with atherogenesis.

Interferon Curbs Mouse Tumors

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observed an effect on protein and RNA synthesis in treated cells, we do not understand the implications of this."

The frequently sought cancer-virus link does not seem to apply in this case. Infectious, tumor-inducing virus has not been found in any of the tumors used (although adenovirus 12 specific antigen is present in the adenovirus-induced tumors).

(Not much antiviral action would be expected in this system in any case, investigators explained, because the antigens of transformed cells are not affected by interferon and even the adenovirus is relatively resistant to interferon action.)

They suggest the anti-tumor action may be related to a general enhancement of the body's immunological response.

Other Possibilities

A second possibility is that the drug (poly I:C) may act directly on the tumor. In support of this, there is the preliminary evidence mentioned by Dr. Levy that treatment of mouse cells with poly I:C does modify RNA and protein synthesis.

A third possibility is that poly I:C produces changes in the blood supply to the tumor, leading to tissue death.

All of these possibilities are being examined. Meanwhile, clinical dosage schedules are being developed. A major problem is determining whether a dose large enough to be effective in humans will be nontoxic as well.

If the drug is determined to be safe for human use, it could possibly be used against such tumors as cancer of the lung and breast which have not responded well to other drugs.

Co-authors of the report are Lloyd Law, PhD, and Alan Rabson, MD. Drs. Levy and Baron are staff members of the National Institute of Allergy and Infectious Diseases; Drs. Law and Rabson, of the National Cancer Institute.

Dr. Levy presented the paper at the Third International Congress on Interferon in Lyon, France.