Aspirin for Reducing Cancer Metastases?

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Distant metastases are the principal cause of death from cancer. Many animal experiments in the last 25 years have shown consistently that distant metastases can be significantly reduced by anticoagulants and fibrinolytic agents. Since aspirin inhibits platelet function and increases fibrinolytic activity in humans, it may be effective in preventing metastases in cancer patients. It is suggested that aspirin be offered as an option to cancer patients who are at risk for distant metastases.

Cancer Deaths From Distant Metastases

According to the estimates of the American Cancer Society,[1] 385,000 people will die from cancer in the United States in 1977. Using Suit's[2] estimate of the number of deaths from cancer by failure to control the tumor locally, one can conclude that about 300,000 or approximately 75 percent of all cancer deaths are due to distant metastases. This high percentage is even more disturbing if one considers that little progress has been made in increasing the survival of patients with distant metastases in the last decades.

The dismal picture of the high frequency of distant metastases coupled with their unaltered poor prognosis is, of course, the mainspring in the vast effort over the last decades to develop chemotherapy and, more recently, immunotherapy. Unfortunately, the results with these two modalities have not lived up to the expectations. We should therefore be on the lookout for other possible ways of attacking the problem of metastases.

Reduction of Distant Metastases by Anticoagulants and Fibrinolytic Agents

In the USA, four groups have conducted extensive animal investigations in the hope of preventing or at least reducing the incidence of distant metastases. Between 1954 and 1969, the first research team, led by Sumner Wood, Jr.[3-13] at the Johns Hopkins University and Hospital in Baltimore, Maryland, studied the influence of hormones and anticoagulants on experimental metastases from injected cancer cells. Only heparin and dicumarol treatment decreased the frequency of metastases. Lysis of tumor thrombi by fibrinolytic agents was also demonstrated by direct observation and filming of metastases in the rabbit ear chamber.

The second research team worked at the Memorial Center for Cancer in New York under the direction of Eugene Cliffton.[14-21] In a number of papers written between 1961 and 1968, they reported a consistent reduction of distant metastases by anticoagulants and by fibrinolytic enzymes.

The third research team worked at the National Cancer Institute under the direction of Alfred Ketcham[22-29] and reported, from 1962 to 1971, on several studies with three separate experimental tumor-host systems in mice. In all experimental models, anticoagulation induced with dicumarol reduced metastatic tumor dissemination and increased the long-term survival.

Under the direction of Gabriel Gasic[30-32] ,the fourth research team, at the Department of Pathology of the University of Pennsylvania School of Medicine, conducted between 1962 and 1973 studies on the role of platelets in the spread of malignant disease. In 1962, they reported that Vibriocholerae neuraminidase reduces metastases produced by intravenous injection of tumor cells. In subsequent studies, they established that this effect was due to thrombocytopenia caused by this agent and that other thrombocytopenic agents such as antiplatelet serum also reduced the incidence of lung metastases, while agents which increase platelet aggregation such as many [15 to 31] tumors and embryonic fibroblasts increased metastases.

In Europe, Terranova and Chiossone[33] in 1952 in Italy, and Lecour, Oberling, and Guerin[34] in 1955 in France were the first to demonstrate in animals the antimetastatic effects of heparin and dicumarol respectively. The more recent European animal studies were just reviewed in 1976 by Hilgard and Thornes.[35]

The difficulties and risks of the human use of anticoagulants and fibrinolytic agents seem to have hampered clinical applications. However, the few oncologists who tried anticoagulants reported results which seem too good to be true; Thornes[36] states in the summary of his study with 128 cancer patients that "in a controlled trial using continuous oral Warfarin Sodium as maintenance therapy for recurrent cancers, 26 patients (40.6 percent) were alive after 24 months compared to 11 (17.8 percent) of the control group." Elias[37] claims that in his study with 25 inoperable lung cancer patients . . . . "those who received multiple chemo only, showed no tumor regression after 2-5 courses. On the other hand, massive tumor regression was demonstrated histologically, clinically, and radiologically in eight out of nine patients that received heparin and the same chemo." Larsen et al[38] reported in 4 of 11 desolate cancer patients objective improvement and tumor regression.

In summary, all studies (most from well-known research institutions) have shown a consistent and significant reduction of the incidence of distant metastases after the use of anticoagulants, fibrinolytic enzymes, or thrombocytopenic agents.

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Aspirin as Anticoagulant and Fibrinolytic Agent

The credit for being the first to call attention to the anticoagulant properties of aspirin and to apply them systematically in clinical practice belongs to an astute general medical practitioner, Dr. Lawrence L. Craven. In February 1950, in a letter to the editor,[39] in which he reasoned, on the basis of his clinical observations, that aspirin has mild anticoagulant properties and that it might be useful for the prophylaxis of thrombosis and embolism. In this first paper, he also reported on 400 persons whom he had given prophylactically one to two aspirin tablets of 5 grains (300 mg) daily. In 1953 he had enlarged his series to 1,465 persons[40] and in 1956 to 8,000 persons.[41] In the 1956 paper he stated firmly and in bold type that "not a single case of detectable coronary or cerebral thrombosis has occurred among patients, who faithfully adhered to this regimen," that "no major strokes have occurred," and that "no untoward reactions have developed in normal patients during one to ten years of oral administration of aspirin, 5 to 10 grains daily." Craven straightforwardly concluded that "aspirin administration offers a safe and sure method of prophylaxis against thrombosis."

Craven's papers went unnoticed, but five years later, the anticoagulant properties of aspirin were rediscovered by Beaumont and co-workers[42,43] and later by Blatrix[44] in France and Hofmann[45] in Germany.

It took another ten years until the impairment of blood coagulation by aspirin was described in the American literature. In 1964, Gast[46] reported a decrease of the platelet stickiness by aspirin and in 1966, Quick[47] described prolongation of the bleeding time by aspirin. Weiss and Aledort[48] found in 1967 that aspirin inhibits collagen-induced platelet aggregation. In the same year, Evans and his coworkers,[49,50] O'Brien[51] and Davies, Hughes and Tonds[52] reported detailed studies on the effects of aspirin on platelet function. In 1970, Weiss, Danese and Voleti[53] showed that experimentally induced arterial thrombosis in dogs can be prevented by aspirin administration.

Clinical reports of human trials with aspirin to reduce the incidence of thrombosis and embolism, aside from the above-mentioned articles by Craven from 1950 to 1956, were to our knowledge not published until 1971, when Salzman, Harris and DeSanctis[54] reported a controlled study of 169 patients undergoing vitallium-mold arthroplasty of the hip. The results with aspirin were just as good as with warfarin (dicumarol) and significantly better than without treatment. The frequency of bleeding complications was the same in their treated and untreated groups.

By 1971, enough interest was aroused in the use of aspirin as an anticoagulant that clinical trials were considered. In the United States, a special conference was held in 1971 in Houston, Texas, in preparation for a clinical trial. This conference produced a 163-page book, published in 1971 and entitled "Aspirin, Platelets and Stroke: Background for a Clinical Trial."[55] In this book Weiss (p. 126) pointed out that there may be more effective agents than aspirin which inhibit platelet function but that aspirin best fulfills the requirements for clinical trials that a drug must be safe, simple to administer, and its side effects well known. Evans (p. 94) felt that low doses such as one 300 mg tablet of aspirin once or twice a day would be adequate for the anticoagulant effect and that this effect would last for several days. Kantor (p. 125), a rheumatologist, called even six 300 mg aspirin tablets taken daily for years mere "chicken feed"; he stated that this level is achieved in numerous rheumatic patients without any difficulty and that it would not be unreasonable to maintain a large population for a long time on this dose.

Apparently, none of the participants of this conference was aware of the aforementioned studies on the possibility of prevention of cancer metastases by anticoagulants. They also did not seem to be worried about the possible teratogenic, gastric, ototoxic, thyroid hematological, dermatological and endocrine side effects of chronic aspirin use which had been the topic of another conference, "Effects of Chronic Salicylate Administration" held in New York City in 1966,[56] in which aspirin had been considered in detail. The fact that much remained to be learned about aspirin is shown by the 1971 discovery that aspirin inhibits the biosynthesis of prostaglandins.[57]

A new finding of great interest for the antimetastatic potential of aspirin is the 1977 discovery of Moroz,[58] that the fibrinolytic activity of whole blood and of platelet deficient plasma, as measured by 125 Iodine-fibrin assay, increased in human volunteers significantly after ingestion of aspirin.

It is pertinent to review now briefly the clinical trials with aspirin in the treatment of cardiovascular disease, because they demonstrate (1) the safety of chronic aspirin administration and (2) the difficulties to come to conclusions even from carefully planned clinical trials. The first clinical study with aspirin was a small series reported by Heikinheimo and Jarvinen in 1971.[59] Four hundred-thirty men and women in a nursing home, half of them on aspirin, were followed for one year. As might be expected since too few patients were at risk, this study failed to show any effect of aspirin.

The first well-planned American clinical trial was the "Coronary Drug Project Aspirin Study" (CDPA), which was started in late 1972 and terminated in early 1975. A detailed report was published in 1976.[60] The patients recruited were 1,529 people who had a prior history of myocardial infarction (MI). They were randomly given, on a double-blind basis, aspirin therapy (one 324 mg tablet three times a day) or a placebo. Follow-up ranged from 10 to 28 months. Side reactions were not serious and no increase of peptic ulcer was noted. For a summary of the results we quote the last paragraph of the abstract: "Overall mortality was 5.8 percent in the aspirin group and 8.3 percent in the placebo group (an observed difference of 30 percent). This difference is suggestive of a beneficial effect from aspirin in the treatment of post-MI men but not large enough to be conclusive."[60]

Two other large studies which also suggested that there might be beneficial effect from the use of aspirin in myocardial disease were reported prior to the publication of the above trial results in the same issue of the British Medical Journal of March 9, 1974. The first paper by Elwood et al[61] reported a study conducted from February 1971 to September 1973 in South Wales. Daily dosage was one 300 mg aspirin tablet. No patient had to be withdrawn from the study because of side effects and none had a gastrointestinal hemorrhage. In 1,239 men

who had had a recent myocardial infarct, in the aspirin group "a reduction in total mortality of 12 percent at 6 months and of 25 percent at 12 months" was recorded. The abstract calls this "statistically inconclusive" and states that "further trials are urgently required."

The second paper on the subject of MI and aspirin in the same issue was a report from the Boston Collaborative Drug Surveillance Group.[62] Their Study I (1966–1971) involved 776 hospital patients who had a discharge diagnosis of acute myocardial infarction and 13,898 hospital patients with other discharge diagnoses. The relative risk of myocardial infarction was found to be only one-fifth as high for people who took aspirin daily. Study II (1972) revealed that the risk was about half as high in people who took aspirin at least four times a week. The abstract concludes that "the data are consistent with the hypothesis that aspirin protects against this disease. Clinical trials are needed to determine whether this hypothesis is correct."[62]

Another interesting study, stimulated by efforts of the two aforementioned investigations, was reported by Hammond and Garfinkel in 1975.[63] This study was based on the material from a large prospective cancer study in which more than one million questionnaires were collected by volunteers of the American Cancer Society. In this questionnaire, space had been provided for ticking off either (1) aspirin "never," or (2) aspirin "seldom," or (3) aspirin "often." Fifteen percent of the men and nine percent of the women answered "never"; 72 percent of the men and 69 percent of the women, "seldom"; and 13 percent of the men and 22 percent of the women, "often." Unfortunately, "seldom" and "often" were not clearly defined and another questionnaire with more details on aspirin use appears necessary before conclusions can be drawn from this type of study.

In 1976, Jick and Miettienen[64] updated the results of Study I from the Boston Collaborative Drug Surveillance Group.[62] Acute myocardial infarction was found in six of 652 (0.9 percent) of regular aspirin users vs 376 of 7,496 (5 percent) of the control patients. Jick and Miettienen state that "our data on aspirin use does not appear to be biased and we can think of no other factors that might influence the association sufficiently to explain them."[64] Although the authors calculate the difference to be statistically significant at $P = 0.0001$ they term the results only "provocative" and "call for further evaluation of aspirin as a potential preventive agent for thrombotic disease."

Additional trials are in progress in several countries,[65] but no reports are yet available, according to the April 29, 1977 reply from L. Friedman in answer to our inquiry of the Clinical Trials Section of the National Heart Institute in Washington.

In summary, Craven's 1950 observation that aspirin is a safe anticoagulant has been proven convincingly by many studies and there is a good chance that his clinical judgment indicating that aspirin is effective against thrombosis will also be confirmed.

How to Test Aspirin As an Antimetastatic Agent

As shown above, (1) anticoagulants and fibrinolytic agents reduce the incidence of distant metastases and (2) aspirin is a safe anticoagulant and fibrinolytic agent. The challenge therefore is to test the value of aspirin as an antimetastatic agent in animal and clinical studies.

A few preliminary animal studies on aspirin as an antimetastatic agent have been published,[67-72] which we will discuss in detail in a forthcoming paper in connection with our own aspirin studies with the Lewis lung tumor. More animal work is obviously needed with larger numbers and different settings.

A more difficult problem are clinical studies. Controlled clinical trials are difficult to plan and to conduct, especially with aspirin because the widespread use of aspirin can interfere with the results in the control groups. According to Hammond and Garfinkel,[63] only 15 percent of American men and 9 percent of American women never take aspirin. Vane[67] estimates that 100,000 tons of aspirin are produced yearly and that the average aspirin consumption in Great Britain is 100 tablets per person per year. There is also danger that the subjects in the control group learn about the hope for favorable effect from aspirin and take it on their own without revealing it.[61]

How should we, then, go about testing the clinical value of aspirin for reducing cancer metastases? In spite of all obstacles, controlled clinical trials with careful supervision would obviously be the most scientific method.[68] However, they are expensive and time consuming. Since no cancer trials with aspirin are planned to the knowledge of the Clinical Trial Section of the National Cancer Institute,[74] it would also take a long time to get them under way.

We would like to propose another avenue, which is based on the contention that the case for prophylactic use of aspirin is theoretically sound and that the risk of chronic aspirin use is acceptable. If this argument is accepted, any cancer therapist could offer to his patient with local disease the choice of (1) chemotherapy, (2) immunotherapy, (3) aspirin, or (4) no prophylactic therapy. We believe that this would permit quickly and with negligible expense (one aspirin tablet costs less than a penny), a determination of the clinical value of aspirin for the prevention of cancer metastases, since a great number of patients could be entered in such a study.

Which dose should be used in such clinical trials? After studying the above quoted and other literature and considering the habits of cancer patients, we feel that one of the usual aspirin tablets of 300 mg (5 grains) in the morning and another in the evening is a good schedule.

We would like to stress that we do not advocate aspirin as the sole therapy if distant metastases are present. These obviously should be treated by radiotherapy, chemotherapy or surgery as the case demands. We also do not propose the use of aspirin as general prophylaxis for cancer, although this could be considered if the clinical studies show a convincing decrease of distant metastases by aspirin. We see, however, no reason why asprins should not be offered as an option to cancer patients who are at risk of having distant metastases. More than 80 years of clinical experience, as well as the above quoted clinical trials, with aspirin in cardiovascular disease have shown that the side effects of aspirin, while not negligible, are acceptable to patients and physicians. In our opinion, a cancer patient who often needs pain medamentation anyway loses nothing and risks little with chronic aspirin use. And even if there is only a small gain from aspirin, the benefit:risk ratio would be

higher than for any other effective cancer therapy.

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