Thrombosis and Cancer

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Thrombosis and cancer are two main pathological events that may be found separately or together in the living organisms. When they exist together, thrombosis occurs secondary to cancer. Mucin-producing cancers produce frequently thrombosis. The mechanism of action occurs through activation of platelets and coagulation factors and interaction of tumor cells with vascular endothelium. Cancers of pancreas, stomach, colon, ovarium and prostate are the cancers which are frequently associated with thrombosis[1]. In patients with venous thromboembolism, we discover concomitant cancer in 15 to 20 percent of patients[2]. The diagnosis of venous thrombo-embolism is made with clinical, radiological and biological methods. The best biological test is the D-dimer test[3].

Anticoagulant drugs used in the treatment of thrombosis are in two groups: The antagonists of vitamin K and the heparins. The antagonists of vitamin K are effective in venous thrombosis. They should be carefully monitored with prothrombin-time test. The various heparins also are effective in thrombosis. Unfractioned heparin and low-molecular weight heparins may be used for this purpose[4].

Observations made during anticoagulant treatments have shown the benefits obtained in cancer patients. One of the first observations in the subject belongs to Michaels from Canada, who found that oral anticoagulants reduced mortality in cancer patients[5].

Berkarda et al, have shown that warfarin inhibits metastasis formation in mice inoculated with Lewis lung tumor[6]. Table 1 shows that warfarin decreased very significantly lung metastases, although it does not influence the size of the primary tumor. Table 2 shows that late anticoagulation also influences metastases, although to a lesser degree. Table 3 shows that warfarin stimulates cellular immunity in mice, using the paw edema test[7]. It has been discovered also that warfarin and coumarin stimulate cellular immunity in man[8].

At the Medical Oncology Section of Cerrahpaşa Medical School, we treated 447 patients with nonsmall-cell cancer of the lung with warfarin associated to chemotherapy and we observed survival benefit[9]. Similar results have also been published by Zacharski and colleagues[10].

The action of warfarin on lymphocytes has been investigated with electron microscope[11]. It has been shown that warfarin activates normal lymphocytes by increasing the number of mitochondria and the density of nuclear chromation. On the other hand, in the leukemic lymphoblastic cells, warfarin causes bursting and vacuolization of mitochondria. This may mean cell death or apoptosis. The photographs on the left sides

Table 1. Lewis lung tumor: Results in mice at the end of three weeks

Groups of 20 mice	Primary tumor (grams)	Number of lung mets
Control	6.5	126
Heparin	5.9	110
Warfarin	4.2	17
Cyclophosphamide	0.6	80

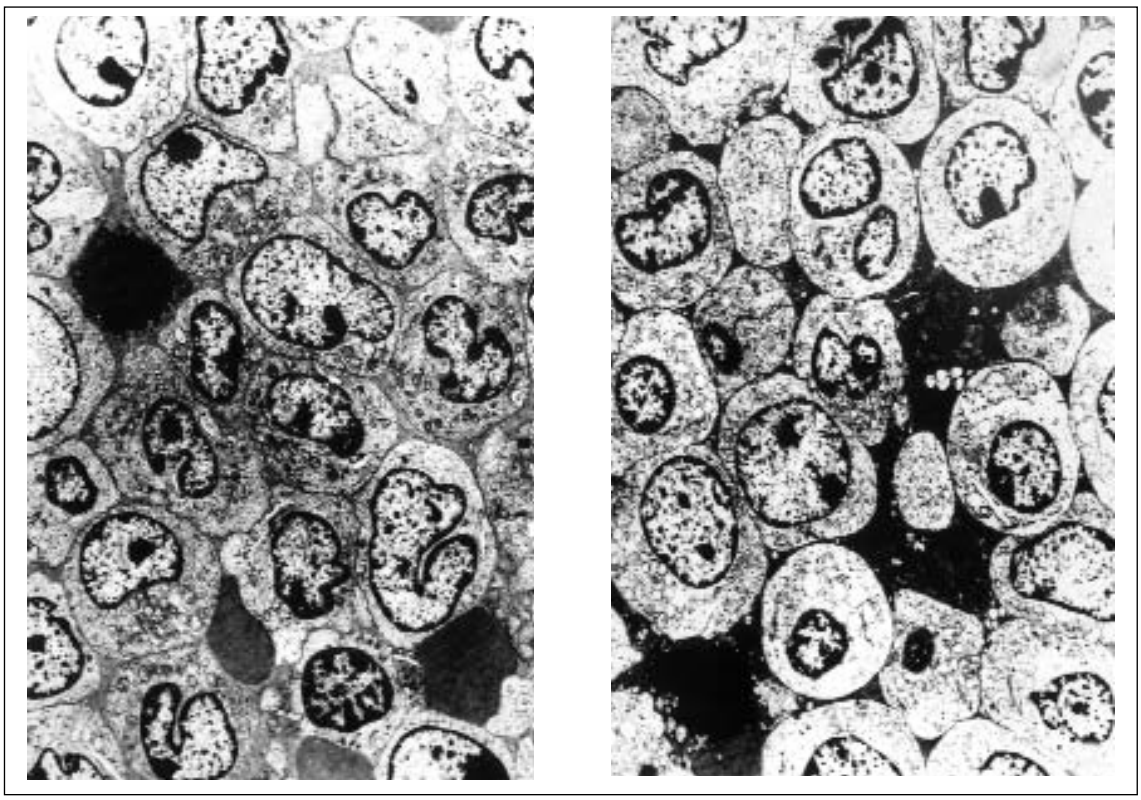

Figure 1. Cells before and after warfarin.

Table 2. Lewis lung tumor: Late anticoagulation

	Number of metastases	
	Controls	With warfarin
End of 2 weeks	144	61
End of 3 weeks	182	128

show the initial cells, while those on right sides show the cells after warfarin.

Our explanation is that warfarin is an electron transferring agent and increase the cellular respiration and stimulate the use of oxygen in the mitchondrium, and the normal cell function is ameliorated. However, cancer cells can not neutralise the superoxide radicals formed in their mitochondria by warfarin and therefore are inhibited.

In parallel with warfarin, it has also been shown that heparin treatment also increases the survival period of cancer patients[12].

Table 3. Effect of warfarin on the delayed hypersensitivity response to sheep red blood cells

		Number of mice/group	Thickness of foot pads + SRBC (x 1/1000 inch)	Thickness of food pads + TRBC (x 1/1000 inch)	Difference (x 1/1000 inch)
Experiment 1:	Warfarin	8	148.4	112.8	33.6 ± 11.1
	Control	8	113.3	103.3	9.0 ± 8.1 p< 0.005
Experiment 2:	Warfarin	8	140.5	101.6	38.9 ± 12.3 0.025> p> 0.01
	Control	4	111.8	100.8	18.0 ± 8.4

Warfarin administration was begun on day 0. On day 2 mice were primed İV with 4 x 10^5 SRBC. On day 6. they were challenged with 50% suspension of SRBC in the right rear foot pad, and 50% suspension in TRBC in the left rear foot pad. Foot pad thickness was measured 24 hours later. SRBC: Sheep red blood cells. TRBC: Toad red blood cells.

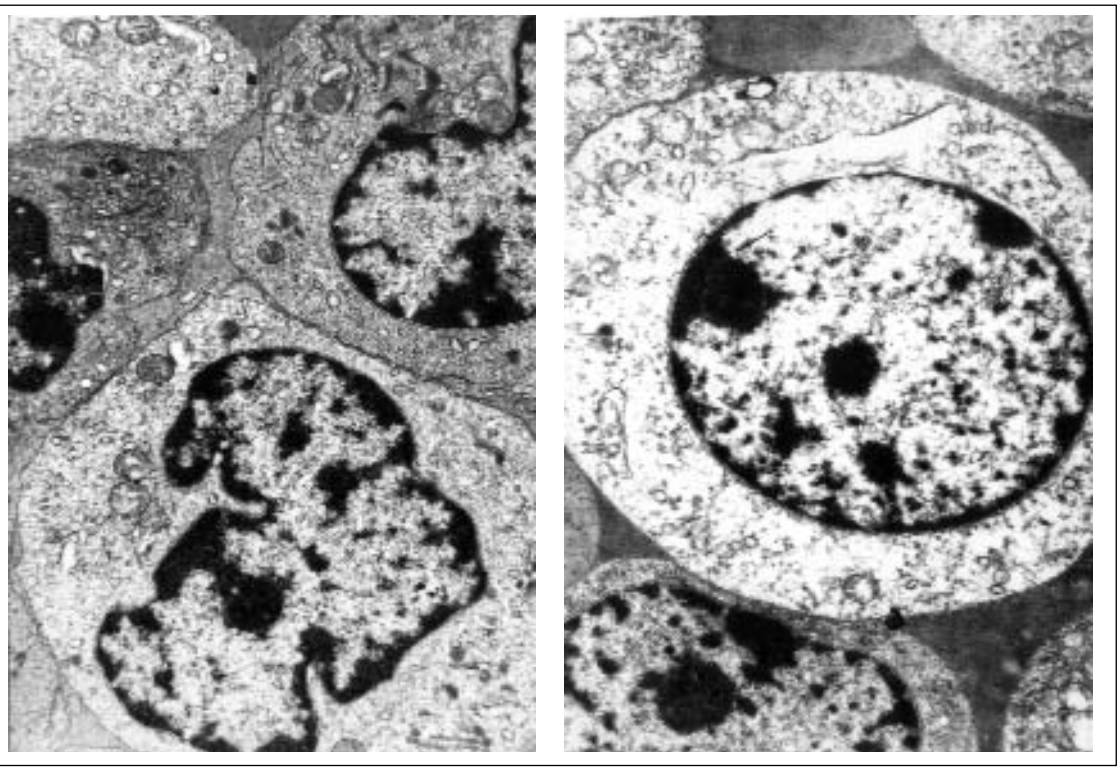

Figure 2. Before and after warfarin.

In conclusion, we think that anticoagulants exert beneficial effects on cancer, while they prevent thrombosis.

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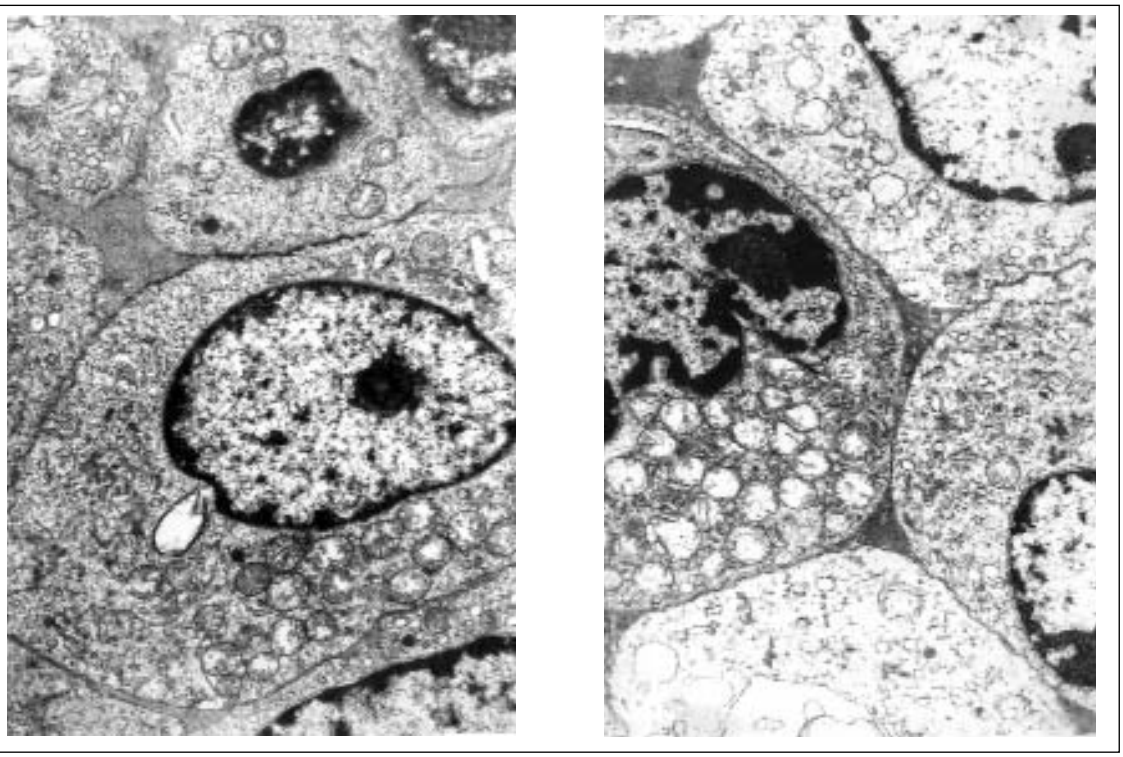

Figure 3. Before and after warfarin.

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