NEW CLINICAL INDICATIONS FOR TRENTAL

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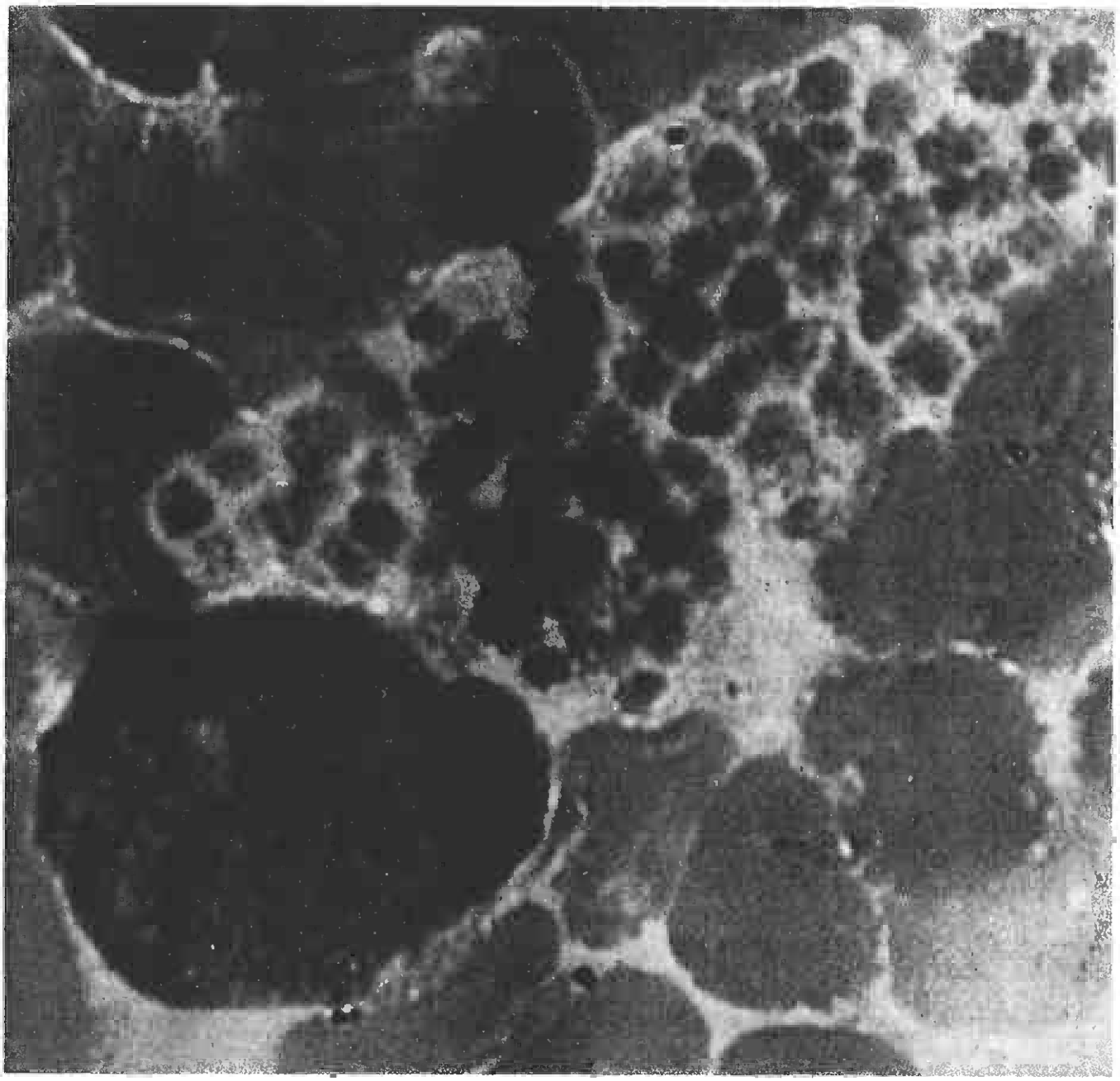
In cancer patients, circulating cancer cells were found to induce aggregation of platelets on these cancer cells (fig. 1). This brings about fibrin formation and formation of complexes consisting of several cancer cells, platelets undergoing viscous metamorphosis and fibrin. The complexes are arrested in capillary beds. Tumor cells grow along fibrin fibers, protected from immunologic forces and chemotherapeutic agents, break through the capillary wall and eventually produce clinically recognizable metastases. It was thought that powerful platelet aggregation inhibitors may prevent this process. For this reason search was undertaken for such agents.



We have developed a method to study platelet aggregation *in vivo* in monkeys (Ambrus, J.L., et al., 1976). An arterio-venous bypass is introduced, which contains a screen with a 20μ pore diameter. As little as 0.1 pgm of ADP or 1.0 pgm of serotonin will occlude the screen with aggregating platelet masses even in a fully heparinized animal. This can be continuously recorded by monitoring the pre-and post-screen pressurely by strain gauges and by examining the screen by scanning electron microscopy. In this system a significant inhibition was detected by pentoxifylline with a linear dose response between 6 and 24 mg/kg (Gastpar, H, et al., 1977) (fig. 2).

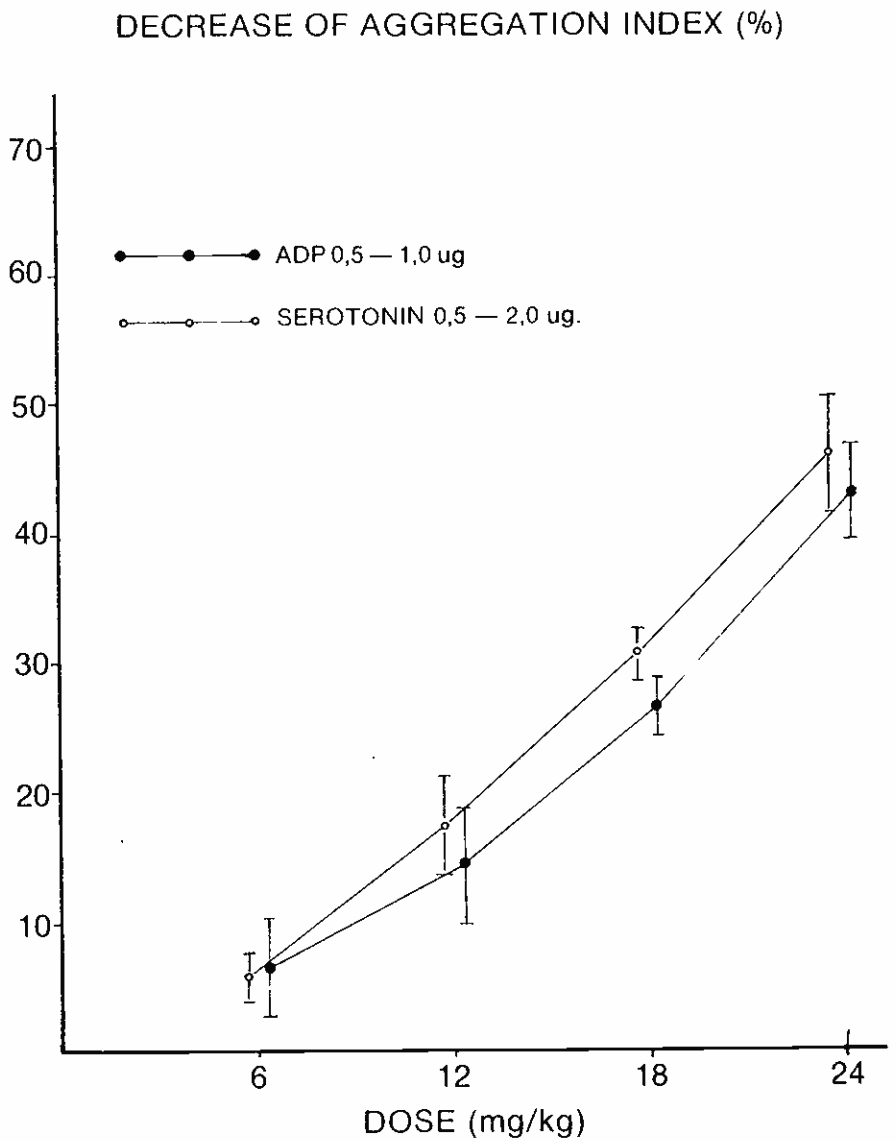


Figure 2: Effect of different doses (6-24 mg/kg) of pentoxifylline on ADP-and serotonin-induced platelet aggregation *in vivo* in stumptailed monkeys *(Macaca arctoides)* Means and standar errors.

A method was developed (Gastpar, H., et al., 1977), to label ascites tumor cells with radio-isotopes and record their circulation time in experimental animals. This was significantly prolonged by platelet aggregation inhibitors. Pentoxifylline was highly active from this point of view (Gastpar, H, et al 1978) (fig. 3). In a series of studies, Gastpar et al (1974, 1974, 1972) found that pentoxifylline can decrease tumor cell induced pulmonary embolization and thrombocytopenia in experimental animals and prevent the adherence of tumor cell complexes to capillary walls in the microcirculation.

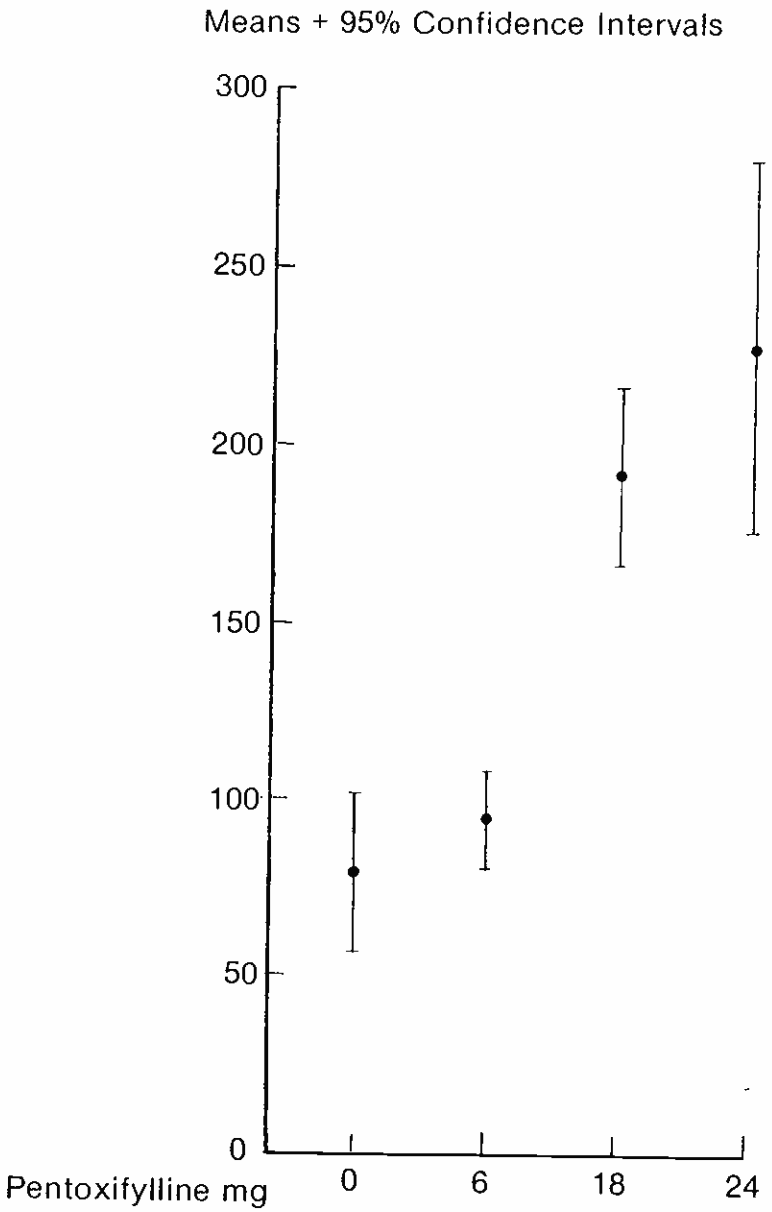


Figure 3. Effect of various doses of pentoxifylline (mg/kg) i.v. 10 minutes before i.v. injection of 2.5×10^7 polyploid Ehrlich ascites tumor cells on circulation time of the latter. Mean circulation times ± 95% confidence intervals are shown in minutes.

In tumor surgery reported "curative" by the surgeon and pathologist, often recurrences occur related to tumor cell mobilization into the circulation during surgery. It was hoped that this could be prevented by platelet aggregation inhibitors, possibly in combination with chemotherapy given after surgery. In a current study, not yet completed, this hypothesis appears to be supported (fig. 4).

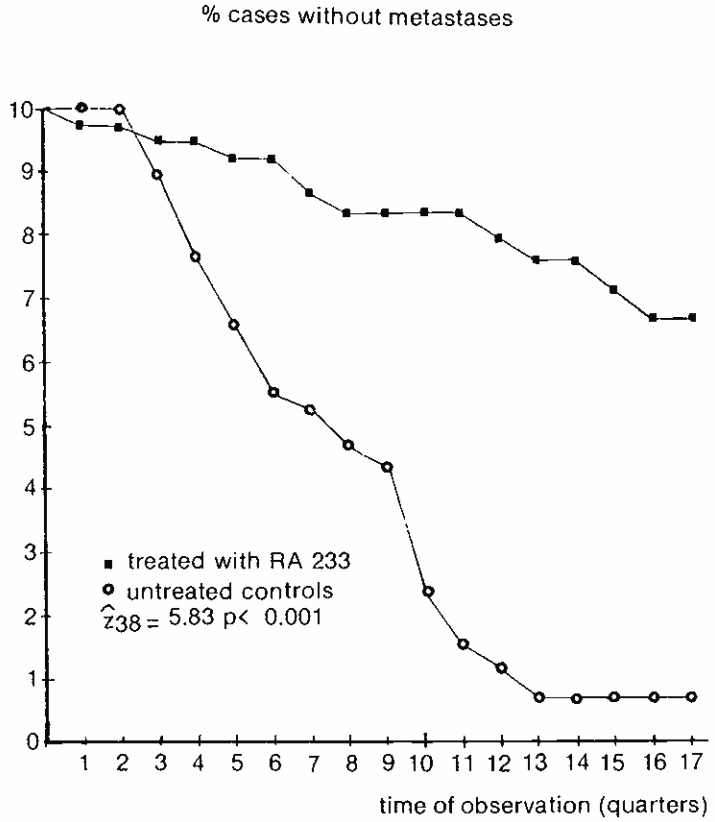


Fig. 4. Percentage of patients operated on for head and neck malignancies following treatment with the platelet aggregation inhibitor RA 233 (250-500 mg t.i.d. per os) or placebo. 38 matched pairs. Statistical evaluation by life table technique of Cutler and Ederer.

In cancer patients thromboembolic complications and disseminated intravascular coagulation (DIC) appear to be important causes of death (Ambrus J.L., et al., 1975). There is a significant correlation between the incidence of thromboembolism and the demonstration by special cytologic methods of circulating tumor cells in the blood stream. Animal studies suggest that these phenomena can be prevented with pentoxifylline (Gastpar, H., et al., 1978). Long range clinical studies are planned. A number of other potential therapeutic benefits are being investigated or presently planned.

A special hematologic problem in the USA is the crisis of sickle cell disease. Pathologic red cell and platelet masses clog the microcirculation producing hypoxia and pain. Because of its platelet aggregation inhibitory effect, red cell deformability increasing and viscosity decreasing effect pentoxifylline may be of important therapeutic benefit.

In arteriography or venography, the x-ray contrast media used appear to increase platelet aggregation and danger of thromboembolism particularly in diabetic patients with abnormal circulating lipid levels. This may be prevented by the incorporation of platelet aggregation inhibitors.

Cardiopulmonary bypass pumps used in cardiac surgery and hemodialysis apparatus cause aggregation and removal of platelets, often resulting in thrombocytopenic hemorrhage. This may be prevented by the use of aggregation inhibitors.

Transient cerebrovascular ischemic episodes appear to be related to platelet aggregation. Similarly platelet aggregation on atherosclerotic vasculature, coronary artery thrombosis, growth of existing clots and recurrence of myocardial infarction may be provented by platelet aggregation inhibitors. Several investigators feel that the atherosclerotic process itself is promoted by platelet aggregation (DeGaetano, G., et al., 1970) and can be prevented by inhibitors.

In malaria caused by *Pl. falciparum*, aggregation of red cells and platelets and microvascular occlusion is at times a serious problem. Study of platelet aggregation inhibitors and red cell flexibility-active agents appears to be indicated.

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