

## GI Intolerance and Nitrofurantoin

Nitrofurantoin, 1-[(5-nitrofurfurylidene)amino]hydantoin, is an important agent in the arsenal of antibacterials used to fight urinary tract infections. Despite proven efficacy, the use of nitrofurantoin has been frequently associated with nausea and vomiting<sup>1</sup>. These effects have limited the use of the drug in some patients, thus denying them its therapeutic potential.

In a recent issue of this Journal, Parrott and Matheson<sup>2</sup> reported that nitrofurantoin can be absorbed when administered rectally in certain suppository formulations. Although absorption was poor, bacteriostatic concentrations (>1:100,000) were achieved in the urine and maintained for up to 4 hr after a 400-mg dose. The authors concluded that: "Persons who exhibit nausea and emesis after oral administration of nitrofurantoin possibly could receive nitrofurantoin therapy by the rectal route." This conclusion may not be justified.

Rectal administration itself will not always alleviate the problem of nausea associated with certain oral medications. If a drug is directly irritating to the GI mucosa, this approach is likely to succeed. However, if the nausea and emetic response caused by a drug are mediated predominantly through an effect on the central nervous system, then these side effects will not necessarily be avoided by using the rectal route.

Nitrofurantoin serves as an example of a drug that produces nausea and vomiting, at least in part, *via* a central mechanism. Support for this contention comes from data showing a relationship between blood levels of the drug and these side effects<sup>3</sup>. Decreased urinary excretion levels are also associated with the decreased incidence of nausea<sup>4</sup>. Furthermore, parenteral administration as an intravenous<sup>5</sup> or intramuscular<sup>6-8</sup> injection also produces nausea and vomiting.

Some success in reducing the frequency of these side effects has been achieved by decreasing the rate of nitrofurantoin absorption. Large crystals, in contrast to microcrystals, of the drug produce more gradual absorption and yet allow the achievement of therapeutic amounts in the urine<sup>3</sup>. This may be the reason macrocrystals of nitrofurantoin tend to produce less GI upset. Food, by delaying absorption<sup>9</sup>, similarly seems to improve GI tolerance.

In the study by Parrott and Matheson<sup>2</sup>, an oral dose (400 mg) of nitrofurantoin (fine, 320-325 mesh) produced gastric upset in four of their original eight subjects. The authors did not report whether nausea was produced in subjects who received the same dose rectally. The absence of nausea, if this were the case, could be the result of the relatively poor rectal absorption observed.

For nitrofurantoin, a reduced rate of bioavailability may uniquely diminish its side effects. These findings<sup>2</sup> should provide a stimulus for further pharmacokinetic and biopharmaceutical studies to improve therapeutics with drugs that may behave like nitrofurantoin.

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Received August 15, 1977.

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## Cancer Cell Aggregates: Temperature Elevation

Currently, there is controversy regarding the relationship of the quantity of blood present in cancerous tissue (*i.e.*, continuous uncontrolled growth in cell aggregates) to the temperature of such tissue. One group maintains that malignancies are characterized by high temperature because relatively large quantities of blood are present in the lesion. The opposing argument holds that elevated temperatures are present in cancerous tissue because the tissue contains a relatively lesser amount of blood. Proponents of this view believe that the lesser quantity of blood has a reduced coolant effect.

We wish to make the following contribution to the discussion. It is a basic fact that blood arrives at any given tumor site at roughly 37°. The temperature of the tumor is higher, approximately 38°. As is known, temperature is an intensive factor. Therefore, regardless of the amount of blood arriving at the lesion, heat can only flow from the higher temperature of the malignancy to the lower temperature of the blood. Given this fact, a greater quantity of blood might provide an increased coolant effect; it cannot be a source of temperature increase. Even if it may be assumed that there is an increased flow of blood to the tumor, in all cases the overall system still involves blood entering and leaving cancerous tissue at a temperature lower than that of the tumor. Thus, blood must act as a coolant.

To explain the temperature of any system, the rate of heat dissipation must be considered as well as heat input. One principal factor influencing the dissipation rate is the nature of the matrix through which heat conduction occurs. Aggregates of normal cells, *i.e.*, flocculated aggregates, contain an open network in which trapped bulk water acts as the coolant. Bulk water as it exists, for example, in blood plasma has excellent cooling properties. Ecanow and co-workers<sup>1-5</sup> proposed that cancer cells are aggregated in a structured matrix, *i.e.*, a coagulated system. In such systems, heat derived from metabolism is conserved because it is lost by conduction at a slower rate than the rate of loss through normal cell aggregates. Thus, because heat is conserved in malignant tissue, its temperature compared to normal surrounding tissue is elevated.

The conclusion to be drawn is that malignant tissue is warmer than normal tissue because: (a) there is more continuous metabolic heat production, (b) the structured intercellular coagulated matrix conserves heat, and (c) malignant tissue simply does not have sufficient blood circulating through it to be cooled to normal temperature.

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Received August 18, 1977.

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