

Communication

# Decreased Norepinephrine Concentration in Normal Tissue Neighboring a Malignant Tumor<sup>1</sup>

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## ABSTRACT

We observed in five adenocarcinomas that norepinephrine as well as nerve fibers were absent from tumor tissue. The number of nerve fibers in normal tissue neighboring the tumor was normal. In contrast, norepinephrine concentration was decreased in normal tissue immediately surrounding tumor and increased in a stepwise fashion with the distance from tumor. Since there is evidence that some catecholamines possess antitumor activity, we suggest that depletion of catecholamines and perhaps other neurotransmitters in normal tissue neighboring a tumor may be of importance for invasion and accelerated malignant growth.

## INTRODUCTION

We have shown previously that norepinephrine is absent from malignant tumors, presumably because they lack sympathetic innervation (1). In the present study, we report the influence of a malignant tumor on the catecholamine content and the number of nerve fibers in normal tissue neighboring a tumor.

## MATERIALS AND METHODS

Five large bowel adenocarcinomas were studied immediately after surgical removal from 5 subjects (2 males and 3 females; mean age, 54 years; range, 44 to 68 years). None of them had been treated with cytostatic agents.

A biopsy of the whole intestinal wall with a diameter of 7 mm was taken (a) from the central part of the tumor, (b) from macroscopically normal tissue immediately surrounding tumor at both proximal and distal border, and (c) at 1-, 2-, and 3-cm intervals from tumor border in both directions. Each biopsy was divided into 2 approximately equal parts. One part (50 mg) was used for determination of norepinephrine and epinephrine. The other part was used for microscopic examination to verify the presence or absence of malignant tissue in each specimen. Tumor tissue containing necrosis was excluded from analysis. Another biopsy was taken close to the first biopsy for histological examination of the nerve fibers. The tissue was stained with hematoxylin and eosin (Merck AG, Darmstadt, Germany), and the number of nerve fibers in nonmalignant and malignant tissue was quantified by point counting (4) and expressed in percentage of total tissue area.

Norepinephrine and epinephrine were determined by a double isotope derivative technique (2). The reproducibility of

norepinephrine determinations in tissue specimens expressed as the coefficient of variation is 5% (6). Tissue specimens were immediately cut into small pieces added to 10 times the volume of iced perchloric acid (0.4 N) containing ascorbic acid (2 mg/ml; proanalysis; Merck), homogenized, and frozen until the analysis could be performed. Each sample was homogenized in 1-min periods for 15 min. Further homogenization did not increase the catecholamine content of tissue specimens.

## RESULTS

Norepinephrine and nerve fibers were absent from all specimens of tumor tissue (Chart 1). In normal tissue, nerve fibers covered approximately 0.75% of total tissue area, and the number of nerve fibers was not influenced by tumor distance. In contrast, norepinephrine concentration was decreased in normal tissue immediately surrounding tumor and increased in a stepwise fashion with the distance from tumor approaching

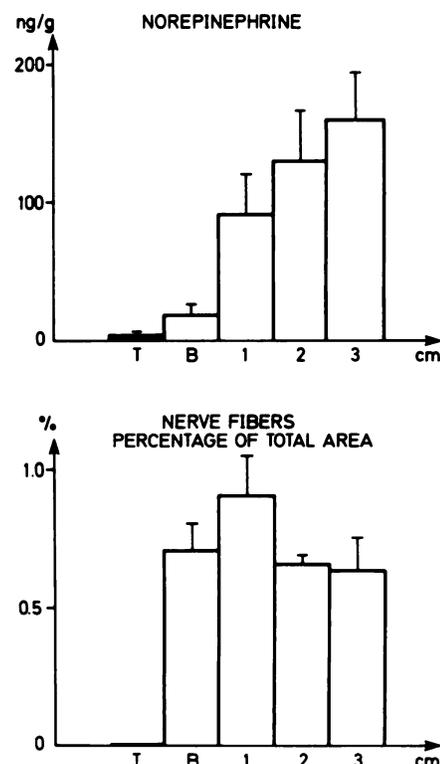


Chart 1. Mean norepinephrine concentrations (ng/g tissue) and mean number of nerve fibers expressed as percentage of total tissue area in specimens from central parts of 5 large bowel adenocarcinomas (T), from normal tissue immediately surrounding tumor (B), and at 1-, 2-, and 3-cm intervals from tumor border. Values obtained in proximal and distal directions were averaged. Bars, S.E.

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normal values of approximately 150 ng/g at 2 and 3 cm (Chart 1). Analysis of all norepinephrine values obtained in normal tissue by analysis of variance and by Kruskal-Wallis nonparametric test (7) pointed to real differences between norepinephrine concentrations at different distances from tumor ( $p < 0.01$ ). Epinephrine was present in small amounts in nonmalignant tissue and constituted on average 3% of the norepinephrine concentration. The distribution of epinephrine was similar to that of norepinephrine.

## DISCUSSION

Although malignant tumors cause angiogenesis (5), they do not stimulate the growth of nerve fibers. It is possible that tumor cells secrete a factor which inhibits catecholamine biosynthesis, but we cannot exclude a number of alternative explanations for the decreased catecholamines in normal tissue neighboring a tumor. This abnormality, however, is unlikely to be due to a destruction of sympathetic nerve fibers because the nerve fibers examined appear unaffected and without degenerative changes at points approaching the tumor border. Dopamine was not measured, but we have previously found a

close correlation between norepinephrine and dopamine concentrations in nonmalignant tissue (6).

There is evidence that some catecholamines possess anti-tumor activity (3). We suggest that depletion of catecholamines and perhaps other neurotransmitters in normal tissue neighboring a malignant tumor may be a prerequisite for invasion and accelerated growth. This hypothesis is currently under investigation.

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