

5. A. M. Ugolev, Investigation of the Digestive Apparatus in Man [in Russian], Leningrad (1969).
6. M. D. O'Donnel, M. I. McGeeney, and O. Fitzgerald, Enzyme, 19, 129 (1975).

BIOCHEMICAL CRITERIA OF SENSITIVITY AND RESISTANCE OF GASTRIC TUMORS TO 5-FLUOROURACIL

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Because of the biochemical differences between experimental tumors sensitive and resistant to 5-fluorouracil (5-FU) [1, 2], it was decided to undertake corresponding investigations on human gastric carcinoma tissue.

EXPERIMENTAL METHOD

Gastric carcinoma tissue was obtained in the cold state after removal from patients admitted to a Regional Cancer Dispensary. The intensity of accumulation of $[6-^3\text{H}]\text{-5-FU}$ (specific radioactivity 104-192 GBq/mole, Czechoslovakia) in tumor tissue RNA was studied after incubation for 30 and 60 min. The tissue was then washed and homogenized in the cold. The acid-soluble fraction and lipids were extracted from the homogenates and DNA was separated from RNA [6]. Radioactivity of the samples was determined on a Mark III scintillation counter (from "Nuclear Chicago," USA).

Alkaline phosphatase (ALP) activity was determined [7] in tumor homogenates, and uridine kinase [5] and thymidine kinase [3] activity in partially purified homogenates by a radioisotope method. Protein was determined by Lowry's method [4].

EXPERIMENTAL RESULTS

Incorporation of $[6-^3\text{H}]\text{-5-FU}$ into RNA of different tumor cells took place with different intensities, and it resembled very closely incorporation of labeled 5-FU into experimental tumors sensitive and resistant to the compound. In some tumors incorporation of 5-FU into RNA took place in the same intensity as in tumors sensitive to 5-FU, and in others, with the same intensity as in tumors resistant to 5-FU [2]. In agreement with these data, the tumors studied were divided on the basis of incorporation of $[6-^3\text{H}]\text{-5-FU}$ into RNA into those sensitive and resistant to the compound (Table 1).

Activity of ALP, uridine kinase, and thymidine kinase was studied in these same tumors, and in tumors sensitive to 5-FU it was found to be significantly higher than in resistant tumors (Table 2).

The correctness of our views on sensitivity of gastric tumors to 5-FU on the basis of biochemical tests was confirmed by clinical trials.

In the period from 1976 through 1978 we studied 123 tumors removed from patients at the Regional Cancer Dispensary. After the operations these patients received prophylactic chemotherapy with 5-FU. All these tumors were divided on the basis of ALP activity into those sensitive (58) and resistant (65) to the compound. ALP activity in tumors sensitive and resistant to 5-FU was 20.88 ± 0.60 and 11.13 ± 0.67 $\mu\text{moles p-nitrophenol/mg protein/min}$, respectively ($P < 0.001$).

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TABLE 1. Incorporation of [6-³H]-5-FU into RNA (in nanomoles/min/mg RNA) of Gastric Tumor Tissue Cells (M ± m)

Tumors	Number of tumors	Incorporation of [6- ³ H]-5-FU into RNA		P
		after 30 min	after 60 min	
Sensitive	8	1,89±0,08	3,57±0,21	<0,001
Resistant	12	1,29±0,14	1,46±0,11	<0,05

TABLE 2. Enzyme Activity in Gastric Tumors Sensitive and Resistant to 5-FU, Determined on the Basis of Incorporation of 5-FU into RNA and of ALP Activity (M ± m, n = 8)

Enzyme	Enzyme activity		P
	in tumors sensitive to 5-FU	in tumors resistant to 5-FU	
ALP	22,97±1,97	13,42±0,78	<0,001
Uridine kinase	1984±137	693±101	<0,05
Thymidine kinase	3425±426	1526±190	<0,001

Legend. ALP activity shown in μ moles p-nitrophenol/min/mg protein, kinase activity in cpm/mg protein.

The late results of treatment of these patients were studied. Effectiveness of the prophylactic chemotherapy with 5-FU was judged from the survival of the patients after 4-8 years depending on the sensitivity of the tumors removed to 5-FU (on ALP activity). Of the 58 patients with tumors sensitive to the compound, 33 (57%) were still alive 4-8 years after the operation, whereas among patients with tumors resistant to 5-FU only 11 (17%) survived.

On the basis of these results, besides the test of incorporation of labeled 5-FU into gastric tumor tissue RNA, the test based on determination of ALP activity can also be recommended for determination of individual sensitivity of gastric tumors to 5-FU.

LITERATURE CITED

1. A. K. Belousova and G. K. Gerasimova, Vestn. Akad. Med. Nauk SSSR, No. 5, 58 (1978).
2. M. P. Shlemkevich, Byull. Eksp. Biol. Med., No. 2, 72 (1983).
3. E. Bresnick and H. B. Thompson, J. Biol. Chem., 240, 3967 (1965).
4. O. H. Lowry, N. J. Rosebrough, A. L. Farr, et al., J. Biol. Chem., 193, 265 (1951).
5. A. Osengo, J. Biol. Chem., 244, 2204 (1964).
6. G. Schmidt and J. Thannhauser, J. Biol. Chem., 161, 83 (1945).
7. W. C. Schneider and G. H. Hogeboom, J. Biol. Chem., 198, 155 (1952).