visible with the fluorescence method by FALCK and HILLARP in human heart ventricles (GENNSER and OWMAN, to be published).

In the older foetus (group A) the concentration of cardiac noradrenaline in every heart chamber was lower than that reported for adult sub-primate mammals. It was apparent that the pattern of noradrenaline distribution between atria and ventricles seen in adults of other species[1-5] is not attained at this stage of human development.

The activities of MAO and COMT were of approximately uniform magnitude in the different parts of the heart with 2 notable exceptions: the MAO activity of the right ventricle exceeded that of the left ventricle ($p < 0.001$) and the right atrium contained a very low COMT activity compared with the other heart chambers. It was a very conspicuous finding that the major enzyme responsible for the degradation of circulating noradrenaline had a low activity in a region containing the cardiac pacemaker. In the absence of neuronal uptake, inhibition of COMT may cause a significant increase of noradrenaline concentration at the adrenergic receptor sites if the concentration of exogenous noradrenaline is low[12]. It seems reasonable to assume that the neuronal uptake mechanism of noradrenaline (uptake U_2) is relatively ineffective in the sparsely innervated foetal heart during the early half of ontogenesis. The very low COMT activity in the right atrium therefore appears to be of special significance. A local reduction of the ability to metabolize noradrenaline in the sinus region, as suggested by the low degrading enzyme activity in vitro, might be of importance for the adrenergic regulation of the foetal heart rate, before the nerve-receptor function in the sinus node is fully established. A positive chronotropic effect exerted by adrenaline was recently demonstrated already in the very young (and not yet innervated) human foetal heart[13]. Catecholamines (noradrenaline and adrenaline) are present in the human foetal adrenals[14,15] and extra-adrenal chromaffin tissue[14,16] at an early stage. Such non-neuronal amines would reach the receptors of the sinus node by the circulation in far lower concentrations than that of the transmitter released from adrenergic nerve terminals close to the neuromuscular junction. Thus, if non-neuronal adrenergic regulation of the foetal heart rate via the sinus node is present at this developmental stage, the activity of extraneuronal enzymatic inactivation by COMT must apparently be very low or non-existing.

The tissue specimen taken between the ascending aorta and the pulmonary trunk includes the inferior aorticopulmonary glomus. This cluster of argyrophil and probably also chromaffin cells in the human foetus has been attributed a possible chemoreceptor function[17]. The high MAO activity of this region demonstrated in the present study is of interest in view of the assumption that catecholamines are involved in this mechanism[17,18].

Zusammenfassung. Die Konzentration von Noradrenalin und die Aktivität der MAO und COMT wurde in verschiedenen Teilen des menschlichen foetalen Herzens bestimmt. Die Ventrikel der Herzen (bis zu 12 Wochen alt) waren sehr noradrenalinarm. Die COMT-Aktivität des rechten Vorhofs war bis zur Mitte der Schwangerschaft viel niedriger als die der übrigen Herzgebiete. Die COMT- und MAO-Aktivität im Gewebe des Spatium zwischen der Aorta und der Arteria pulmonalis lag ungefähr in der gleichen Grössenordnung wie die der Ventrikel.

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[12] A. J. KAUMANN, J. Pharmac. exp. Ther. *173*, 383 (1970).
[13] G. GENNSER and E. NILSSON, Experientia *26*, 1105 (1970).
[14] R. E. GREENBERG and J. LIND, Pediatrics *27*, 904 (1961).
[15] W. v. STUDNITZ, Scand. J. clin. Lab. Invest. *22*, 185 (1968).
[16] G. GENNSER and W. v. STUDNITZ, Scand. J. clin. Lab. Invest. *24*, 169 (1969).
[17] J. D. BOYD, Br. med. Bull. *17*, 127 (1960).
[18] This study was supported by grants from the Medical Faculty, University of Lund, and from Hulda Almroth's Foundation.

Normalization by Nucleotides of Impairments in Deamination of Nitrogenous Compounds in Liver of Tumor-Bearing Mice

Monoamine oxidase activity was decreased[1] in liver of mice with ascites carcinoma. In tissues of the tumor-bearing animals lipid peroxides[2] accumulated, which resemble oxidized oleic acid. Treatment with oxidized oleic acid[3,4] or with ergosterol peroxide[5] of highly purified monoamine oxidases inhibited deamination of monoamines and, at the same time, caused reversible transformation in catalytic properties of the enzymes: the latter acquired abilities to deaminate diamines, polyamines, AMP, lysine and other nitrogenous compounds. If a similar transformation occurred in tumor-bearing mice we could expect that the decrease in monoamine oxidase activity in their liver will be accompanied by appearance of (or increase in) deamination of putrescine or AMP.

Cells of Ehrlich ascites carcinoma were obtained at the 7th day of development of the tumor and inoculated i.p. (about 10^7 cells per each animal) to white (10–20 g) mice. Isolation of mitochondria and estimation of the deamination rates were performed as described previously[6].

In liver mitochondria of the tumor-bearing mice deamination of tyramine or serotonin was decreased, deamination of AMP was sharply increased and an ability to de-

[1] M. KHUZHAMBERDIEV, V. Z. GORKIN and I. E. ELPINER, Vopr. med. Khim. *18*, 294 (1972).
[2] E. A. NEYFAKH and V. E. KAGAN, Biokhimiya *34*, 511, 692 (1969).
[3] Z. I. AKOPYAN, L. N. STESINA and V. Z. GORKIN, J. biol. Chem. *246*, 4610 (1971).
[4] I. V. VERYOVKINA, M. M. ABDEL SAMED and V. Z. GORKIN, Biochim. biophys. Acta *258*, 56 (1972).
[5] L. V. TATYANENKO, R. I. GVOZDEV, O. I. LEBEDEVA, L. V. VOROBYOV, V. Z. GORKIN and V. A. YAKOVLEV, Biochim. biophys. Acta *242*, 23 (1971).
[6] V. Z. GORKIN, Z. I. AKOPYAN, I. V. VERYOVKINA, L. I. GRIDNEVA and L. N. STESINA, Biokhimiya *34*, 140 (1970).

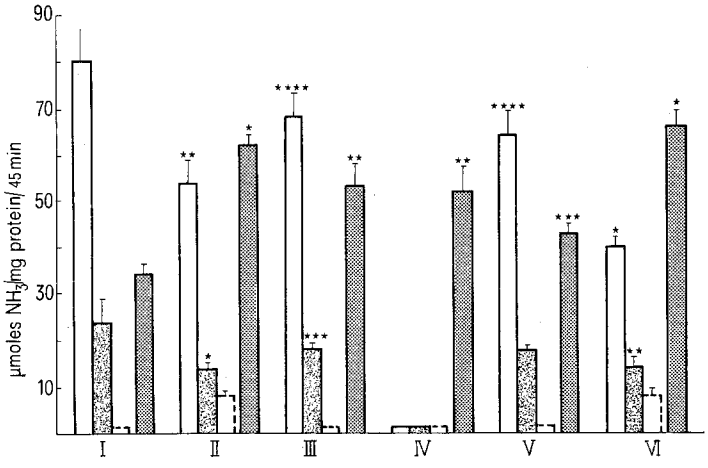

Fig. 1. Deamination by mice liver mitochondria under normal conditions (I) and at the 8th day of development of Ehrlich ascites carcinoma (II) of tyramine (white), serotonin (shaded), putrescine (dotted) and AMP (black bars); effects of: α-tocopherylacetate (III, 490 mg/kg in 2% Tween-40, i.p., daily injections during 6 days beginning at the 2nd day after transplantation of the tumour), indaneamine[7] (IV, 50 mg/kg, s.c., 2 h before the transplantation and then injections every 24 h during 8 days), adenosine-3′-monophosphate (V) and adenosine-5′-monophosphate (VI). Both nucleotides were injected i.p. (600 mg/kg, 2 h before transplantation and then 1 injection every 18 h during 8 days. Mean values ± standard error from 5–6 experiments are presented. Statistically significant difference as compared with control: $p < 0.001$*, 0.01**, 0.02***, 0.05****.

aminate putrescine appeared (Figure 1, II). In nuclear membranes[8] we observed similar phenomena. Content of lipid peroxides in the tumor-bearing mice liver was 136 ± 12 neqv./g of lipids (the normal value was 10 ± 2). Injections of α-tocopherylacetate decreased the content of lipid peroxides to 44 ± 5 neqv./g of lipids. This was accompanied by slight increase in tyramine deamination, and a decrease in AMP or putrescine deamination (Figure 1, III). But the general state of the animals was not improved. Similar results were noted in experiments with a monoamine oxidase inhibitor indaneamine[7] (N-methyl-N-2-propynyl-1-indaneamine), which prevented completely appearance of putrescine deamination and – partially – the increase in AMP deamination (Figure 1, IV). Adenosine-3′-monophosphate (Figure 1, V), contrary to adenosine-5′-monophosphate (Figure 1, VI), markedly decreased deamination of AMP, partially normalized the monoamine activity and prevented deamination of putrescine in the tumor-bearing mice liver. Quite identical effect was caused by another structural analogue of AMP-adenosine-2′(3′)-monophosphate, which was a competitive inhibitor of AMP deamination by mitochondria, pretreated with oxidized oleic acid[6].

Injections of the structural analogues of AMP to the tumor-bearing mice improved their general state, decreased content of tumor cells in peritoneal cavity and increased average duration of survival (Figure 2).

Our data suggest that an increase in AMP deamination[6] in diseases accompanied by lipid peroxides accumulation[9,10] may be pathogenetically important, and that some nucleotides (structural analogues of AMP) may be used for unspecific therapy of these diseases under experimental conditions[11].

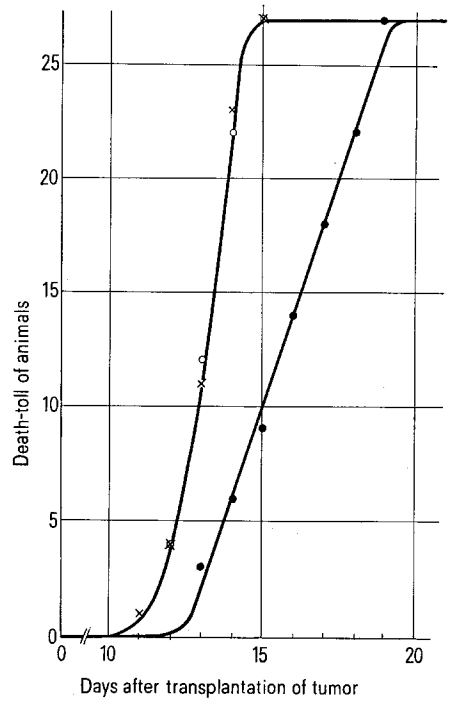

Fig. 2. Effect of nucleotides on survival of mice in Ehrlich ascites carcinoma. Each experimental group comprised 27 animals. 0.9% NaCl (○), AMP (×) or adenosine -2′(3′)-monophosphate (●) were injected i.p. (see legend to Fig. 1).

ВЫВОДЫ. Структурные аналоги АМФ аденозин-2′(3′)- или -3′-монофосфат частично нормализуют нарушения дезаминирования азотистых соединений в печени мышей-опухоленосителей и удлиняют выживаемость этих животных.

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30 May 1972.

[7] C. F. Huebner, E. M. Donoghue, A. J. Plummer and P. A. Furness, J. med. Chem. *9*, 830 (1966).
[8] V. Z. Gorkin, Experientia *27*, 30 (1971).
[9] Z. I. Akopyan, N. V. Blazheievich, I. V. Veryovkina, V. Z. Gorkin, O. V. Syomina and V. B. Spirichev, Int. Z. VitamForsch. *40*, 497 (1970).
[10] Z. I. Akopyan, V. Z. Gorkin, Y. B. Kudryashov and O. V. Syomina, Radiobiologiya *10*, 826 (1970).
[11] V. Z. Gorkin, Z. I. Akopyan, A. A. Kulygina and T. A. Zeinalov, Biull. exp. Biol. Med. *N11*, 42 (1971).