on the side surfaces of adjacent cells. In the oxynticopeptic cells of the glands, observed both in transverse (figure 3) and in longitudinal (figure 4) sections with respect to the lumen of the tubular glands, the CA is localized on the basal and lateral surfaces of the cells. The dark lines, in conclusion, clearly indicate where the reaction is present and where it occured.

These results disagree with the findings of Gay et al.[3,4] who, by means of immunohistochemistry, concluded that the CA activity was localized only in the mucous membrane cells and that hydrochloric acid is not produced by the gland cells. These results are therefore consistent both with the Toner[14] hypothesis and with ours[9].

The electron microscope observations show, in fact, that the apical cell membrane of the glandular cells is smooth, without microvilli. In addition the junctional complex among neighbouring cells is localized close to the base of the cells and the basement cell membrane shows invaginations whose extention increases after stimulation with histamine[14]. The lateral surface which is also the boundary surface, in addition, contains several microvilli which increase the surface. Furthermore this surface may be used for secretion owing to the basal position of the junctional complex. By mean of this mechanism a surface increase (almost six times according to Toner) is obtained. This is almost twice as great as the one which is caused by the presence of intracellular canaliculi in the mammalian parietal cells (3 times according to Hally[16]). For this reason Toner[14] considers the space between the oxynticopeptic cells as equivalent to the intracellular canaliculi of the oxyntic cells.

It is also worth while pointing out that an increased surface has been observed also in the oxynticopeptic cells of other vertebrates[17–19], and that this increased surface is considered to be fundamental for an acid secretion to take place.

In the mammalian oxyntic cells, which certainly produce HCl, the CA activity is typically localized in the intracellular canaliculi at the level of microvilli. For this reason it may be concluded that the distribution of the enzyme on the surface of the oxynticopeptic cells of fowls, described in the present paper, is a histochemical proof of the fact that the 'intracellular space' between the oxynticopeptic cells and the 'intracellular canaliculi', characteristic of the oxyntic cells, play the same role. This, in conclusion, shows that the oxynticopeptic cells determine acid secretion.

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Effect of tranexamic acid on progress of experimental tumours and on DNA-synthesis[1]

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Summary. The fibrinolytic inhibitor tranexamic acid affects certain experimental tumours; it prolongs survival (Lewis lung adenocarcinoma), decreases tumour weight (C3H breast carcinoma), and inhibits ascitic production (AH 130 rat hepatoma). However, it does not significantly influence DNA-synthesis in cell suspensions prepared from the same tumours.

Cytostatic drugs directly or indirectly impair the DNA-synthesis of malignant cells. They also inevitably act on the normal cells, which limits their therapeutic value and makes the search for points of attack in other enzyme systems necessary. Certain cells of mammalian tissues in culture produce hardly-detectable amounts of stable plasminogen activator or none at all, but if they are transformed by oncogenic viruses or carcinogenic substances they release abundant amounts of this activator[2,3]. Furthermore, it has been shown that in organ cultures of normal human ovarian tissue only trace amounts of plasminogen activator are released, while malignant tumours originating from the same organ release large amounts in such cultures[4]. This activator has been shown to be immunologically identical with the plasminogen activator in urine, i.e. urokinase[5], but not with the activator released from the vessel walls into the blood stream[6]. Such activators have been found in the advancing front of invasive carcinoma[7–9] and are thought to be of importance for the fibrinolytic process necessary for the proliferation of tumour vessels[9].

We report here that the fibrinolytic inhibitor tranexamic acid given to animals with certain experimental tumours prolongs survival, decreases the tumour weight and inhibits ascitic production, but does not significantly influence DNA-synthesis in cell suspensions prepared from the same tumours.

Material and methods. 20 C57 black mice were given 5 million cells of Lewis lung adenocarcinoma s.c. resulting in a 100% tumour take. To 10 of them tranexamic acid was given in the drinking water, 0.5 g/kg b. wt/day, and their survival was compared with that of the controls.

20 C3H mice were given 3 million cells of C3H breast carcinoma s.c. From the day of inoculation tranexamic acid was given to 10 of them in their drinking water (0.1 g/kg/day for 20 days). Compared to the C57 black mice the dosage was reduced because of diarrhoea as a side effect. After this period the animals were sacrificed and the circumscript tumours dissected out.

20 Sprague Dawley rats were inoculated with AH 130 rat hepatoma cells. From the day after the inoculation tranex-

amic acid was given by mouth to 10 rats in a dose of 0.5 g/kg b. wt/day in their drinking water or injected i.p. in the same dose. 10 rats served as controls. The animals were sacrificed on the 10th day after inoculation and ascitic fluid was collected.

The effect of tranexamic acid on DNA-synthesis was investigated in cell suspensions of Lewis lung adenocarcinoma, C3H breast carcinoma and AH 130 rat hepatoma by determination of the amount of ^{3}H-TdR incorporated. A previously described method was used[10]. The tumour material was pressed through a Borell net piston[11], washed and suspended in Parker 199. The suspension was preincubated for 3 h at 37 °C with or without tranexamic acid and subsequently incubated for 1 h with tritiated thymidine. The cells were dissolved in a Soluene-based scintillation fluid and the radioactivity was read in a Packard Tri Carb spectrometer 3310. The amount of incorporated ^{3}H-thymidine was referred to the number of tumour cells, estimated as the amount of DNA according to the indole method[12,13] and the effect of tranexamic acid was expressed in a logarithmic form so called a-values[14].

Results and discussion. 3 weeks after inoculation with Lewis lung adenocarcinoma the C57 black mice treated with tranexamic acid had well demarcated tumours, while the controls had large ulcerating tumours. The mean survival of the treated animals was 35 ± 2 (SD) days, compared with 28 ± 2 days for the controls.

The weight of the C3H breast tumours was constantly lower in animals receiving tranexamic acid, 1.76 ± 0.07 g, compared with 2.01 ± 0.08 g in the controls. No such effect was found in an identical experiment carried out with 20-methylcholanthrene-induced sarcoma. In agreement with this, Peterson[15,16] found that tranexamic acid, given in a 5% solution in the drinking water to C3H mice inoculated with mammary carcinoma decreased the tumour growth weight significantly. The growth rate of a 20-methylcholantrene induced sarcoma was not influenced.

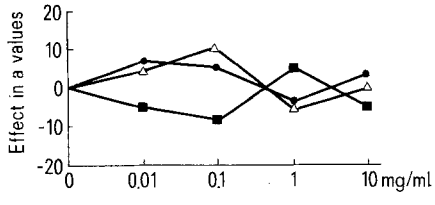
The table shows that the production of ascitic fluid was significantly lower in Sprague Dawley rats with AH 130 rat hepatoma receiving tranexamic acid from the day after inoculation than in the controls. The body weight as a parameter of general toxicity was reduced from a mean of 243 to a mean of 225 g but was unchanged in the controls. It should, however, be pointed out that the amount of ascitic fluid was measured by aspiration from the sacrificed animals.

It is clear from the figure that tranexamic acid had no significant effect on DNA-synthesis in cell suspensions of Lewis lung adenocarcinoma, C3H breast carcinoma or AH 130 rat hepatoma even in a concentration of 10 mg/ml.

Malignant tumours posses thromboplastic properties, that result in the formation of a fibrin network, which serves as a matrix for the proliferation of tumour vessels[17]. Residual fibrin has then to be removed and this is effected by the fibrinolytic properties of the tumour in a way analogous with the process in tissue repair. Studies in cell culture[18-20] and with experimental tumours[15,16] and clinical observations[21,22] suggest an antineoplastic effect of protease inhibitors. Tranexamic acid mainly prevents binding of plasminogen and plasmin to fibrin and is a competitive inhibitor of plasminogen activation, but it also has a weak direct action on the plasminogen activator as well as on plasmin[23,24]. This antifibrinolytic action of tranexamic acid in the absence of significant influence on DNA-synthesis might explain its effect on the C57 black mice inoculated with Lewis lung adenocarcinoma and the retarded growth of C3H breast carcinoma. Furthermore, it is known that plasmin can activate the complement factor Cl to Cl-esterase[25] and also cleave the complement factor C3[26] with increased cell membrane permeability as a result. Depressed formation of plasmin by tranexamic acid might thus in part explain its effect on the production of ascitic fluid on the rats inoculated with AH 130 rat hepatoma cells. The present experiments have thus shown an antineoplastic effect of tranexamic acid on experimental tumours without any significant influence on the synthesis of DNA. Inhibition of the action of the tumour plasminogen activator might open up a new way to interfere with tumour growth.

Effect of tranexamic acid on ascitic fluid (mean ± SD, ml) in Sprague-Dawley rats inoculated with AH 130 rat hepatoma

Route	Tranexamic acid	Controls
Per os	24 ± 4.0	52 ± 6.0
i.p.	46 ± 5.2	82 ± 4.7



Effect of tranexamic acid on the ^{3}H-thymidine incorporation in cell suspensions of Lewis lung adenocarcinoma (●), C3H breast carcinoma (■) and AH 130 rat hepatoma (△).

1 Acknowledgment. This study was supported by grants from Malmö Allmänna Sjukhus and the Swedish Medical Research Council (B79-17X-04523-05B).

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