substances, called chalones[7–10], inhibit DNA synthesis without affecting RNA or protein synthesis. They are tissue-specific but not species-specific.

A non-specific inhibitor of cell growth identified as a methyl-glyoxal analog has also been reported[3,4].

The inhibitor of the RNA synthesis isolated at our laboratory has a MW lower than chalones and higher than ketoaldehydes. There are also marked differences in their mode of action. Methyl-glyoxal and other α-ketoaldehydes seem to interact with SH groups, inhibiting cell proliferation by interference with protein synthesis and, only moderately affect DNA and RNA synthesis[3,4]. All known chalones have been found to inhibit DNA synthesis, while the inhibitor described herein affects primarily RNA synthesis, thus initiating a series of events leading to the inhibition of DNA synthesis and cell death.

The presence of a negative feedback mechanism which is capable of regulating cell growth through inhibition of RNA synthesis has not been previously reported. The inhibition of RNA synthesis may, however, be of significance in the control of malignant growth since differences in RNA metabolism have been found between normal and cancer cells[11].

The results indicate that, indeed, a cytotoxic factor for CML cells is present in human spleens. In addition, a line of CML cells is made available for the first time[12].

Resumen. En este trabajo se describe la purificación de un inhibidor de la síntesis de ARN que afecta secundariamente la síntesis de ADN y actividad mitótica. El factor ha sido aislado de ocho bazos humanos, comprendiendo dos de enfermos con leucemia mielocítica crónica (LMC) dos con hiperesplenismo primario, y cuatro de personas sanas, en los cuales se efectuó la esplenectomía por ruptura traumática del bazo. El inhibidor esplénico posee fuerte citotoxicidad sobre células en cultivo provenientes de enfermos con LMC. Estas células tienen el cromosoma de Philadelphia. El inhibidor esplénico tiene un peso molecular de alrededor de 1,000 y es probablaemente un péptido o glicopéptido.

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Inhibition by Terephthalic Acid of Spontaneous Mammary Tumorigenesis in Mice

It is generally believed that spontaneous mammary tumors in mice are more resistant to chemotherapy than transplanted experimental tumors. None of several antitumor agents involving 5-FU and mitomycin-C, which are widely used for clinical purposes, showed any inhibitory effect on the autografts of spontaneous mammary tumors in Swiss mice[1]. Terephthalic acid (TPA) has been found in rats to prevent *p*-dimethylaminoazobenzene (DAB) metabolizing enzymes in the liver from the decrease of activities by DAB, and to result in suppression of protein-bound dye formation, although TPA did not increase the activities of these enzymes under the normal conditions[2,3]. TPA encouraged the growth of the fowl when it was fed on undernutritional food[4]. No toxicity of TPA was ascertained in mice[5]. These results strongly suggest an important role of TPA in maintenance of homeostasis of the body. The present experiment was carried out in order to investigate whether or not TPA

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Mammary tumor incidence in each group

Group	Total No. of mice examined	Mammary tumor incidence at each months of age (%)[a]												
		4	5	6	7	8	9	10	11	12	13	14	15	16
Control	116	1.7 (2) [113]	6.9 (8) [105]	20.7 (24) [86]	37.1 (43) [61]	51.7 (60) [44]	64.7 (75) [17]	72.4 (84) [17]	75.0 (87) [12]	77.6 (90) [9]	81.0 (94) [5]	81.0 (94) [5]	83.6 (97) [2]	85.3 (99) [0]
TPA	31	0 (0) [28]	0 (0) [28]	3.2 (1) [25]	9.7 (3) [23]	16.1 (5) [19]	32.3 (10) [14]	41.9 (13) [10]	45.2 (14) [9]	48.4 (15) [8]	51.6 (16) [6]	58.1 (18) [4]	61.3 (19) [3]	64.3 (20) [0]
Significance of difference between groups by χ^2-test		NS	NS	$P < 0.01$									$P < 0.05$	

[a] Mammary tumor incidence = (Cumulative number of mice with tumors / Total number of mice examined) × 100. All the mice had mammary tumors or died by the end of 16 months. ( ), Cumulative number of mice with tumors; [ ], Number of surviving mice without tumors.

inhibits the appearance of spontaneous mammary tumors in mice when given continuously as a supplement to the diet.

Materials and methods. C3H/He female mice maintained in the authors' laboratory were used. After weaning at 23–25 days of age, the control and TPA groups were fed the commercial diet (CA-1: CLEA Japan Inc., Tokyo) only and the same diet supplemented with TPA (Teijin Ltd., Tokyo) in the proportion of 0.5%, respectively, ad libitum throughout their lives. At 70–80 days of age, one female was mated with one male and the concurrent pregnancy was planned until the sixth lactation or mammary tumor appearance. Each female was checked for palpable tumors every 7 days till 16 months of age when all the mice had tumors or died.

Results and discussion. As shown in the Table, mammary tumor incidence was significantly lower in the TPA group than in the control group after 6 months of age, and the rate of increase of tumor incidence was markedly suppressed during 10–13 months in the TPA group. These results clearly indicate that TPA feeding inhibits the spontaneous mammary tumorigenesis in mice. The average tumor ages were 9.9 ± 0.6 (S.E.) and 7.8 ± 0.3 months in the TPA and control groups, respectively, and the difference between groups was statistically highly significant ($P < 0.001$). No difference between groups was observed in the pattern of estrous cycle, in the growth during the virginal stage, in any of the items examined as the indices of reproductive ability (the interval between mating and parturition, the litter size, the average weights of pups on days 0, 12 and 20, the growth rate of pups and the rearing rate) and further in the ages of mice that died without tumors. Intratumor injection of TPA had no effect on the growth of Ehrlich carcinoma (solid form)[6]. The data obtained herein suggest the host-mediated antitumor effect of TPA through its homeostatic action on the body, while the precise mechanism has not yet been understood. The differences between groups of the mammary tumor incidence were smaller after 14 months than before 13 months, although they were still statistically significant ($P < 0.05$). They may be due to the insufficient ability of TPA in maintenance of the homeostasis of the body in these older ages. CAME and MOORE[7] and POTMESIL and GOLDFEDLER[8] reported the direct inhibitory effect of interferon or its inducer on mammary tumorigenesis in mice. The mode of action of TPA on mammary tumorigenesis is probably quite different from that of interferon.

Zusammenfassung. Die Fütterung von Terephthalsäure hemmt die Bildung von spontanen Tumoren der Milchdrüse bei der Maus.

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The Production of Plasminogen Activator During Perfusion of Isolated Rabbit Kidneys

As in the renal venous blood in vivo there is increase in fibrinolytic activity[1], also during perfusion of isolated kidneys plasminogen activator appears in the outflowing fluid from the renal vein[2]. The amount of the activator detected per unit of time can be used for calculating the enzyme liberation rate of the kidney. The value determined does not depend on the perfusion rate but is dependent upon the composition of the perfusing fluid and the preserved metabolism of the organ[3].

These studies were undertaken with the aim of clarifying the effect of the composition of the perfusing fluid and of the preserved metabolism of the organ on the quantity of plasminogen activator liberated as well as on the amount of the activator retained in the organ after perfusion as compared with the level of the enzyme in the kidney determined before examination.

Materials and methods. The kidneys were removed from the rabbits anaesthesized with uretane after previous heparin administration. The isolated organ was placed in a receptacle in 0.9% NaCl at 37 °C. The perfusing fluid,

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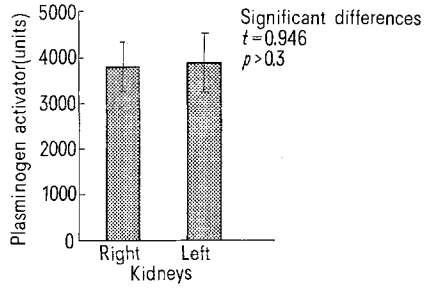

Fig. 1. Plasminogen activator in the 6 pairs of the rabbit kidneys: right kidneys — 342 ± 76 U/g; 3814 ± 520 U/organ; left kidneys — 365 ± 56 U/g; 3887 ± 662 U/organ. Significance differences in activator concentration: $t = 0{,}444$; $p > 0{,}6$.

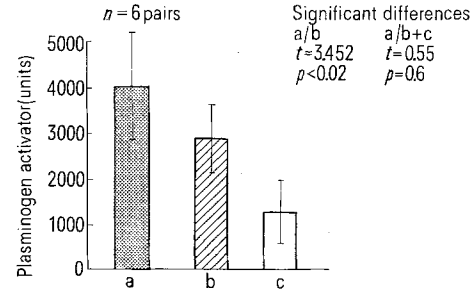

Fig. 2. Plasminogen activator in the kidneys perfused with Tyrode's fluid: a) kidneys before perfusion: 385 ± 63 U/g; 4065 ± 1176 U/organ; b) kidneys after perfusion: 261 ± 59 U/g; 2896 ± 768 U/organ; c) fluid after perfusion: 1306 ± 735 U.