sium excretion (U_KV) showed an increase of about 30% of the control value during the 8-thio cAMP administration.
The table summarizes the results obtained with nine 8-substituted derivatives of cAMP. Paired values represent data obtained before and 20–30 min after the initiation of the infusion of each compound. As was the case with 8-thio cAMP, the other derivatives also increased RBF with only a slight effect on BP and GFR. Apparent diuretic, natriuretic and kaliuretic effects were observed with 6 of the 9 derivatives: 8-hydroxy cAMP, 8-thio cAMP, 8-azido cAMP, 8-methoxy cAMP, 8-methylthio cAMP and 8-dimethylamino cAMP.

Discussion. The nine different 8-substituted derivatives of cAMP we examined here were found to increase RBF with essentially no effect on BP, in agreement with the findings using cAMP[13,14]. In general, an increase in intracellular cAMP in smooth muscle cells is associated with a relaxation of the muscle[15]. Muneyama et al.[3] who studied the relative stability of some 8-substituted cAMP derivatives to enzymatic hydrolysis found that these derivatives are fairly resistant to degradation by rabbit kidney phosphodiesterase. In addition, it was apparent that some were inhibitors of cAMP phosphodiesterase. The above findings suggest that the vasodilative effects of the 8-substituted derivatives may be related to an intracellular substitution for cAMP or an increase in cAMP by inhibition of cAMP phosphodiesterase. However, the present study does not rule out the possibility that metabolites of the 8-analogues may mediate the renal vasodilating effects of these compounds, as adenosine is reported to produce renal vasodilation in a manner similar to that seen with cAMP[13].
Though all the 8-substituted derivatives increased RBF, only some produced moderate diuretic and natriuretic effects. A similar discrepancy was also reported between the effects of cAMP and dibutyryl cAMP (DBcAMP) on urine formation[14,16]. We have no explanation for these discrepancies; however, it is noteworthy that DBcAMP, as well as some of the 8-substituted derivatives, is more resistant than cAMP to hydrolysis to 5′-adenosine monophosphate by cyclic nucleotide phosphodiesterase[17], and that an inhibition of phosphodiesterase has been suggested[18].
The 8-analogues induced diuretic and natriuretic effects with little effect on GFR, thus suggesting the renal tubular effects of these derivatives. In fact, the parent nucleotide cAMP may inhibit electrolyte transport in the proximal tubule[7,8,10,11]. Differences in diuretic potency among these derivatives probably reflect the intracellular concentrations of these compounds in the tubules.

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Antipyrine metabolism in cancer patients

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Summary. The metabolism of antipyrine was studied in cancer patients. Antipyrine elimination might be decreased in cancer patients. Increase in antipyrine half-life is not primarily due to the presence of a tumor but rather to the nutritional status and liver function of an individual.

The effects of the presence of some tumors on the hepatic microsomal enzymes that metabolize drugs have been studied extensively in animals[2,3]. These studies show that inhibition of hepatic drug metabolism is observed in tumor-bearing animals[2,3]. In contrast with animal studies, little is known about drug metabolism in humans with cancer. Ambre et al.[4] reported a shortened plasma elimination half-life of antipyrine in patients with lung cancer compared to normal volunteers. In contrast with the findings of Ambre et al.[4], Tschanz et al.[5] recently demonstrated a decreased rate of drug clearance in lung cancer patients. Clinicians treating patients with cancer must realize that neoplasia may influence drug disposition and metabolism markedly since patients usually receive a number of anticancer agents that are metabolized by hepatic microsomal enzymes. Our study was conducted in a series of patients with gastric carcinoma and carcinoma of the pancreas to compare systematically the activities of hepatic microsomal enzyme system in patients with localized carcinoma and in patients with disseminated carcinoma and in control subjects, using antipyrine half-life ($t_{1/2}$) as an index of drug metabolism, and to evaluate the microsomal enzyme system in humans with cancer.
Materials and methods. 4 groups of subjects were chosen for

the study. 5 in-patients with peptic ulcer acted as control sujects (group 1). 19 patients with histologically proved gastric carcinoma or carcinoma of the pancreas were studied, 13 of 16 patients with gastric carcinoma were judged to have localized diseases (group 2) and 3 had distant and widespread metastasis (group 3). 3 patients had localized carcinoma of the pancreas (group 4). After overnight fasting, antipyrine (1.0 g) was given orally with 300 ml of water. No food was permitted for 3 h thereafter to ensure complete absorption of the drug. Blood was drawn into tubes containing sodium heparin 4, 6, 9, and 12 h after drug administration. Plasma antipyrine level was determined by the method of Brodie et al.[6]. Log. concentration vs time was plotted, and the elimination rate constant (Ke), plasma concentration at zero time (Co), and $t_{1/2}$ were calculated by the method of least squares. The apparent volume of distribution (aVd) and metabolic clearance rate (MCR) were determined from the following equations:

$$t_{1/2} = 0.693/Ke \quad (1)$$

$$aVd = dose/Co \quad (2)$$

$$MCR = aVd.Ke \quad (3)$$

None of the patients was receiving chemotherapy and immunotherapy at the time of this study. All the subjects studied were males and had smoking habits, and none were chronic ethanol abusers.

Results. The mean age, body weight, height, creatinine clearance, serum albumin, and total bilirubin are summarized in table 1. The age, the weight, and the height were similar in all the groups. The mean creatinine clearance in group 3 was lower than that in group 1, but not significantly different. Serum albumin concentration in group 3 was significantly lower than in group 1 ($p < 0.01$). Total bilirubin in group 4 was significantly higher than that in group 1 ($p < 0.01$). Pharmacokinetic data are shown in table 2. The mean half-life in group 3 was significantly longer than that in group 1 ($p < 0.001$). All of the Patients with disseminated gastric carcinoma showed a significantly prolonged half-life when normal range is expressed as mean ± 2 SD of control subjects. Although the mean half-life in groups 1 and 2 were not significantly different, 5 patients from group 2 exhibited a significant trend toward prolonged levels. The mean half-life in group 4 was also longer than that in group 1 ($p < 0.05$). Similary the mean MCR in group 3 was significantly lower than that in group 1 ($p < 0.02$). The mean NCR in group 4 was also significantly lower than that in group 1 ($p < 0.05$). The mean aVd was not significantly different between the groups. Some reports have suggested that malnutrition and impared liver function may lead to decreased levels in the activity of hepatic microsomal enzymes in humans[7,8]. The relationship between half-life of antipyrine and albumin concentrations in patients with gastric carcinoma was studied. A significant negative correlation was observed between the half-life and albumin concentrations in patients with gastric carcinoma ($n = 16$, $r = -0.519$, $p < 0.05$).

Discussion. Hepatic microsomal enzyme system can be stimulated or inhibited by age, cigarette smoking, drugs, hormones, and a variety of environmental agents. Therefore, we performed this study with control subjects matched to the patients on the basis of alcohol intake, smoking, age, sex, body weight and height. It is clear that the rate of antipyrine elimination is retarded in cancer patients with hypoalbuminemia or hyperbilirubinemia. The mean plasma half-life in disseminated gastric carcinoma patients was almost twice as long as that in control subjects. Results of our experiments agree fairly well with the clinical study of Tschanz et al.[5] in which a decreased rate of antipyrine clearance in lung cancer patients was demonstrated.

The mechanism of the changes in microsomal enzyme activities in patients with malignant diseases is not clear at present. In animals, hepatic microsomal enzyme activities are decreased in the presence of some tumors. There was a good correlation between the tumor size and enzyme inhibition. Furthermore, injection of tumor extracts into normal rats produced an inhibitory effect. These results indicate that humoral factors from neoplasia may inhibit drug disposition and metabolism in animals. In human studies, a decreased activity of hepatic microsomal enzymes was observed in individuals suffering from protein malnutrition and in debilitated chronically ill patients[7]. Patients with disseminated gastric carcinoma have a poor dietary protein intake and show hypoalbuminemia. A decrease in hepatic microsomal enzyme activities in patients with gastric carcinoma could theoretically be due to the nutritional status because of malnutrition in patients. In fact, a significant negative correlation was observed between the half-life of antipyrine and the albumin content, as mentioned

Table 1. Anthropometric data in patients with gastric carcinoma and carcinoma of the pancreas, and controls

Group	No. of subjects	Age	Height (cm)	Weight (kg)	Creatinine clearance (ml/min)	Serum albumin (g/dl)	Total bilirubin (mg/dl)
1 (controls)	5	48.8 ± 15.8*	162.6 ± 9.2	54.2 ± 12.5	121.2 ± 38.5	4.1 ± 0.4	0.46 ± 0.16
2 (gastric carcinoma: localized)	13	55.2 ± 9.2	163.5 ± 6.4	56.8 ± 8.7	113.1 ± 37.9	4.1 ± 0.3	0.56 ± 0.32
3 (gastric carcinoma: disseminated)	3	64.3 ± 7.9	160.3 ± 4.8	50.7 ± 9.0	72.7 ± 10.8	3.0 ± 0.1**	0.89 ± 0.79
4 (carcinoma of pancreas)	3	64.7 ± 12.3	162.7 ± 6.1	59.0 ± 5.7	95.6 ± 38.7	3.4 ± 0.8	13.41 ± 5.56**

* Mean ± SD; ** significantly different from group 1 ($p < 0.01$).

Table 2. Pharmacokinetic data on antipyrine in patients with gastric carcinoma and carcinoma of the pancreas, and controls

Group	No. of subjects	Co (μg/ml)	aVd (l/kg)	MCR (ml/h/kg)	$t_{1/2}$ (h)
1 (controls)	5	26.7 ± 4.0*	0.735 ± 0.147	52.6 ± 13.4	9.3 ± 1.5
2 (gastric carcinoma: localized)	13	27.9 ± 4.5	0.655 ± 0.145	49.2 ± 22.7	11.0 ± 3.7
3 (gastric carcinoma: disseminated)	3	29.5 ± 4.7	0.695 ± 0.115	22.8 ± 5.0**	21.5 ± 3.2***
4 (carcinoma of pancreas)	3	28.0 ± 4.3	0.633 ± 0.148	26.6 ± 3.9****	17.1 ± 5.0****

* Mean ± SD; ** significantly different from group 1 ($p < 0.02$); *** significantly different from group 1 ($p < 0.001$); **** significantly different from group 1 ($p < 0.05$).

above. Furthermore, the mean half-life in group 2 was not significantly longer than in group 1, and the mean half-life in group 4 with hyperbilirubinemia was significantly longer than in group 1, although there was no significant difference in serum albumin from group 1. These observations indicate that the increase in half-life of antipyrine was not primarily due to the presence of tumor, but rather to the nutritional status and liver function of the individual. In contrast with our results, Ambre et al.[4] demonstrated a shortened plasma elimination half-life of antipyrine in lung cancer patients. This discrepancy indicates that changes in the metabolic fate of antipyrine in cancer patients might not be due to cancer itself. It is particularly important that the metabolism of antipyrine might be altered in patients with cancer since patients with cancer usually receive a number of drugs that are metabolized by the hepatic microsomal system[9].

Anticancer agents are seldom used alone but rather in combination with other anticancer agents. Anticancer angents and extracts from bacteria are also currently used in combination for the chemoimmunotherapy of a number of neoplastic diseases. Recent studies reported that extracts from bacteria cause a significant reduction in hepatic microsomal enzyme activities[10-12]. Decreased activities of hepatic microsomal enzyme have been reported in rats treated with some anticancer agents[13]. It may be predicted that these substances such as antimetabolic and alkylating agents, which interfere with the synthesis of nucleic acids, would inhibit hepatic microsomal enzyme. On the other hand, it has been reported that a long-term administration of 6-mercaptopurine in humans increased the requirement for warfarin[14]. These results suggest the possibility that 6-mercaptopurine might induce hepatic microsomal enzyme. Because of these observations, information about changes in drug metabolism in patients with cancer deserves serious consideration.

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Antiprolactinic ergolines

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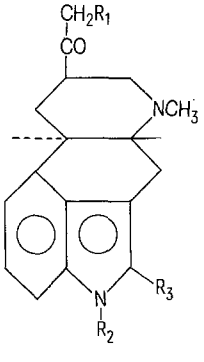
Summary. The synthesis and the antiprolactin activity of a group of 8-acetylergolines are reported.

The inhibitory activity toward prolactin secretion of ergot alkaloids and their derivatives has been recently reviewed[1]. In the present note we report the preliminary data on the preparation and antiprolactin activity of a group of new ergolines (**I**) bearing a hydroxyacetyl side chain present in many biologically active compounds, synthesized in the course of our extensive screening program for semi-synthetic ergot derivatives[2,3].



(1)

Chemistry. The synthesis of 8-acetylergoline (No. 1) has been previously reported[4], however all attempts to brominate it to **I** (R_1 = Br; R_2 = R_3 = H) yielded only 2-bromoacetylergoline and 2,13-dibromoacetylergoline. Reaction of diazomethane with the mixed ethoxyformic anhydride of dihydrolysergic acid in tetrahydrofuran yielded a diazoketone (m.p. 163–165 °C) that by reaction with ethanol[5] in the presence of BF_3 etherate gave the ether No. 14 and by reaction with HBr gave the required bromoketone **I** (R_1 = Br; R_2 = R_3 = H)[6]. Condensation of the rather unstable bromoketone with the sodium salt of an appropriate carboxylic acid or with the acid itself in the presence of KF in DMF[7] yielded the esters No. 3 ÷ 10 and 16. Likewise the phenyl ether No. 15 was obtained by condensation of the bromoketone with sodium phenate in refluxing ethanol. Chlorination of compound 7 to give compound 12 was performed with sulphuryl chloride in the presence of BF_3 etherate complex[8] whereas the 2-bromo compound 11 was obtained by treatment of compound 7 with NBS[9] in dichloroethane at 45 °C. Compound 2 was obtained by methanolysis at room temperature of compound 4 in the presence of a trace of triethylamine and compound 13 was prepared by