serotonin-like compounds: 5-ethoxytryptamine[7] and 5-methoxy-SAS[8] (5-methoxytryptamine molecule in which the nitrogen atom in the ring is substituted by sulphur). In the available literature there are 2 short reports on the first substance indicating its high toxicity[4] and modest radioprotectiveness[6], while there are no data on 5-methoxy-SAS.

In the present experiment, due to the restricted amounts of both substances, only one dose of irradiation was applied. Therefore mice (F_1 hybrids of CBA ♂ and C 57 Black ♀) were irradiated with a distinctly supralethal dose of X-rays, i.e. 1400 R ($LD_{100/30}$ = 950 R). For the same reason, it was impossible to test previously the toxycity of these compounds. The substances in question were administered i.p. 5–10 min before irradiation in doses equimolar to the optimal dose of 5-hydroxytryptamine (50 mg/kg body wt.)[10]. Every experimental group numbered 20 mice. The survival of irradiated animals was followed for 30 days.

The results indicate (Table) that 5-ethoxytryptamine and SAS are protective to the same level. This radioprotective effectiveness apears to be insignificantly lower than that of 5-methoxytryptamine. The χ^2-test for 5-ethoxytryptamine, as compared to serotonin, was not significant. The difference in effectiveness between 5-methoxytryptamine and serotonin is negligible. As for 5-methoxy-SAS, it does not exhibit any radioprotective effect in supralethally irradiated mice.

In spite of the preliminary character of these findings, due to the small number of animals in each experimental group, it could be concluded that the substitution of the hydroxy group in position 5 of the indole ring by a methoxy, ethoxy or mercapto group is without any essential influence on the radioprotective effectiveness. Similarly, in the case of SAS, which has instead of the indole ring a benzothiophen nucleus, protection comparable to that of serotonin was observed. However, if in the molecule of SAS at position 5 the hydroxy-group is substituted by a methoxy group, its radioprotective property, under conditions of supralethally irradiation, completely disappears.

Whole-body irradiation of mice with 1400 R of X-rays ($LD_{100/30}$ = 950 R)

0.28 mM/kg body wt. (i.p.5–10 min before irrad.)	No. of animals	No. of survivors after 30 days	Mean survival time (± S.E.M.) in days
1) 5-Ethoxytryptamine	20	11 (55%)	20.3 ± 2.8
2) 5-Methoxytryptamine	20	15 (75%)	23.9 ± 2.0
3) 5-Hydroxytryptamine	20	17 (85%)	26.6 ± 1.9
4) 5-Methoxy-SAS	20	—	5.3 ± 0.6
5) SAS[a]	20	11 (55%)	20.8 ± 2.2

1):3) - χ^2 = 2.976, n.s. [a] 3-(β-aminoethyl)-5-hydroxy-benzo(b)thiophen (CAMPAIGNE et al.[2]).

To comment these finding it could be stated that all these substances elicit a radioprotective effect mainly through their specific pharmacological activity. Namely, 5-methoxytryptamine[11–13], as well as SAS[14,15], are pharmacologically very active compounds. The above-mentioned toxicity of 5-ethoxytryptamine[4] in the present experiment was not expressed. Some preliminary tests performed with 5-ethoxytryptamine and 5-methoxy-SAS indicate a rather weak pharmacological activity of these two compounds[16].

Future studies concerning the relationship between chemical structure, radioprotective effectiveness, pharmacological and toxicological activity might lead to a better understanding of the radioprotective mechanism of these substances.

Zusammenfassung. Bei Mäusen wurde die Strahlenschutzwirksamkeit des 5-Ethoxytryptamins und 5-Methoxytryptamins mit derjenigen von 5-Hydroxytriptamin, SAS (Benzothiophenverbindung) und 5-Methoxy-SAS verglichen. Die Ergebnisse zeigen, dass die Schutzwirksamkeit des 5-Ethoxytryptamins der des SAS sehr ähnlich ist.

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Apurinic Acid, a Modified DNA with Anticancer Activity

In 1952, TAMM, HODES and CHARGAFF reported the production of a purine-free DNA, termed apurinic acid (APA), after subjecting DNA to mild acid hydrolysis[1]. In place of the detached purine bases, APA has an equivalent number of free aldehydo groups[2]. In view of the finding that exogenous, macromolecular DNA can be incorporated into mammalian cells[3–5], we were prompted to consider whether APA possesses any biological activity. In particular, could APA disturb cell proliferation in vivo?

APA was prepared from herring sperm DNA by a method described in detail elsewhere[6]. Briefly, DNA was acidified to a pH of 2.5, quickly brought to boil, and then

maintained at 100 °C for 2 min. Thereafter, it was rapidly cooled, neutralized, and kept at 0° until the purine bases completely detached. The solution was centrifuged, the precipitate separated on a Sephadex G-25 column from NaCl and the freed purine bases, concentrated, and then freeze-dried for use in the animal experiments. Chemical and physical data attesting to the loss of purine bases and the retention of an unaltered number and sequence of pyrimidine bases have been reported[6].

The anticancer efficacy of APA was tested in a xenografted human colonic tumor system, GW-77[7], and an allogeneic hamster amelanotic melanoma, A.Mel.No.3[8], both growing in the cheek pouches of unconditioned, adult golden hamsters (*Mesocricetus auratus*) of both sexes and weighing 60–70 g. I.p. therapy of APA dissolved in distilled H_2O was instituted at 3 days post transplantation to the cheek pouch for the A.Mel.No.3 tumor, and at 7 days post grafting for the GW-77 tumor, and continued 1–3 times daily for a total of 6 or 7 days. The size of the cheek pouch tumors was measured in three dimensions (length × width × depth) at regular intervals by anesthetizing the animals and everting their pouches, and the difference in the mean increase of tumor size between control and treated tumors calculated at 1 day after conclusion of treatment. Each experimental group consisted of 12–15 hamsters, each in turn bearing 2 cheek pouch tumors. The control animals received the same volume and injection schedule of the drug's vehicle as given the groups receiving APA. A more extensive account of our chemotherapy testing method is available in other publications[9,10].

Preliminary experiments indicated that the optimal dose schedule of APA in the rapidly proliferating A.Mel. No.3 tumor is as frequently divided doses daily, whereas in the GW-77 tumor system APA is equally effective when given either once or twice daily. Figures 1 and 2 demonstrate the tumor growth-curves of 2 typical experiments with GW-77 and A. Mel. No. 3 tumors, respectively, showing the growth-inhibitory effects achieved by APA. Whereas control GW-77 tumors experienced a 12.5-fold increase in size from day 7 through 16 post grafting, the APA-treated ones only increased by a factor of 6.8, thus reflecting a tumor growth-inhibition of 46%. In the case of the faster growing A.Mel.No.3 tumors, increase in tumor size of control vs. APA-treated tumors was 71.6 vs. 22.7 from day 3 to day 9 post transplantation, or 69% tumor growth-retardation. These results have been confirmed in a total of 4 experiments with GW-77 and 7 with A.Mel.No.3. It has been our experience that these levels of tumor growth-inhibition are meaningful when compared to the effects of other known chemotherapeutic agents in these tumor systems.

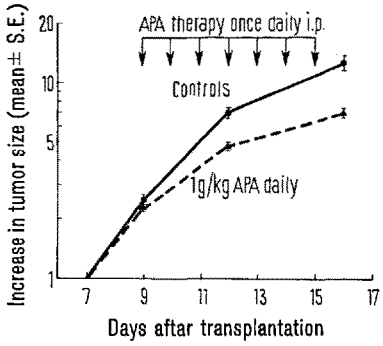

Fig. 1. Experiment comparing growth rate of GW-77 treated with 1 g/kg body weight of APA daily to control tumors, indicating a 46% growth-retardation at 1 day post therapy.

It is important to note, moreover, that although such high doses (0.6–1.0 g/kg body weight daily) were required of APA to achieve these effects, no significant host-toxicity (measured in terms of lethality and body-weight loss) could be found, thus stressing APA's good therapeutic index. Since the GW-77 human colonic tumor system in the hamster is relatively refractory to chemotherapy[11], the antitumor activity shown here for APA, although not curative and only temporary in duration, encourages further experimentation with this compound. The particularly high dose of APA required to achieve these antitumor effects in vivo would appear to limit its use in other animal systems and in man. Nevertheless, its pronounced, selective, inhibition of DNA synthesis[6,12] and of in vitro[12] and in vivo tumor cell proliferation supports it perhaps being the prototype of a new class of anticancer, antiviral, and immunosuppressive agents.

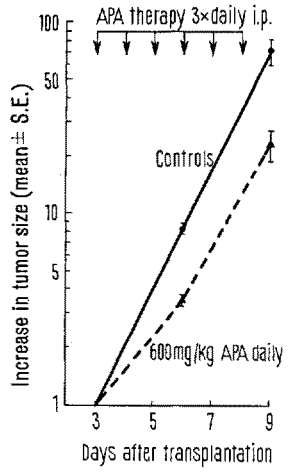

Fig. 2. Effect of 3 × 200 mg/kg daily of APA on growth rate of A. Mel. No. 3 tumors growing in the hamster cheek pouch.

Zusammenfassung. Apurinsäure, ein purinfreies hochmolekulares Desoxyribonukleinsäure-Derivat, hemmt das Wachstum des menschlichen Kolontumors GW-77 und das amelanotische Melanom des Hamsters.

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