sented by KUTTNER et al.[1]. It is possible that the kinetics of efflux of AIBA from the central nervous system is slower than its entrance, in which case it could give the impression of a concentrative process when the plasmatic levels are falling. This type of effect can also be appreciated for thiocyanate[10]. After single intraperitoneal injection of AIBA it was shown that the plasma levels decrease rapidly[8,9].

The AIBA levels in the CSF are lower than in the aqueous humor, indicating a stronger barrier effect for the blood-CSF penetration than for that of the blood-aqueous. In the eye, the barrier effect is obscured by the concentrative process of AIBA by the lens[3-11], and it is possible that the aqueous levels of AIBA are a reflection of the lens-humor relations superimposed on the plasma-humor equilibrium[12].

Résumé. Le passage de l'acide α-amino isobutirique (AIBA) du sang vers le système nerveux central a été étudié en situation constante des niveaux sanguins. Un phénomène de barrière hémato-nerveux est rendu évident par rapport aux autres tissus. On n'a pas observé d'accumulation de l'acide aminé au-dessus des niveaux sanguins après une période de 25 h.

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Investigations on the Effects of Chronically Administered Small Amounts of DDT in Mice

Owing to the relative chemical stability and cumulative property of DDT (*p,p'*-dichlor-diphenyl-trichlorethane) the question permanently arises as to whether the long-term presence of DDT in the organism is injurious to health or not. In connection with this question, the Expert Committee of FAO-WHO[1], among others, found the study of the possible blastomogenic effect of DDT to be of great importance.

Our investigations on the harmful effects of DDT were started in 1963. The plan of work was to give orally small amounts of DDT to animals of a genetically isogenous species for several generations.

Experimental. From the Institute's inbred BALB/c mice strain, 15 bigamous families were selected as P generation. These families were kept together for 6 months. From the descendants of each P generation again 15 bigamous families were selected as F_1 generation. The breeding of further generations was carried out similarly. The animals selected during the 6 month breeding periods were kept isolated according to sex and generation. From July 1963 till August 1965, the breeding of 5 mouse generations had been accomplished. Until this time the experiments were performed with a total of 3766 mice (1797 experimental animals, Group 1; and 1979 controls, Group 2). In September 1965 we isolated 1089 mice: 683 animals originated from Group 1, and 406 animals from Group 2. In both groups, males and females of the 5 generations were represented approximately in the same ratio.

Both mouse groups received the same feed and tap-water ad libitum. The chow of the 2 groups differed only in the DDT content. To that of Group 1, 2.8–3.0 ppm DDT was mixed homogeneously, whereas to that of Group 2, no DDT was added. In the diet of Group 2, DDT was found in amounts of 0.2–0.4 ppm as unavoidable contamination, since at present the natural components of feed contain DDT traces all over the world. Thus the animals of Group 1 consumed on the average 0.3–0.6 mg of DDT/kg body weight (the equivalent of $^1/_{500}$ to $^1/_{1000}$ of the oral LD_{50}), and those of Group 2 0.03–0.05 mg.

The DDT content of the diet was regularly supervised by the method of SCHECHTER and HALLER[2] and that of KOVÁCS[3]. In the organs of the mice, DDT determination was performed by the same methods.

For the determination of the erythrocyte and leucocyte count and the hemoglobin content of the blood, for the preparation of the peripheral blood picture, blood was taken from the tail vein of the animals. The bone marrows were obtained from the femurs. All animals were subjected to biopsy.

For supervision of the isologous homogeneity of our BALB/c strain, the method of skin grafting was used.

Results. During the experiment, started in October 1965, in several animals of the experimental group hematological disorders resembling leukemia were observed. Later on, malignant tumours of different localization and structure also appeared.

Table I shows that in the experimental group of 684 mice, 24 animals (3.51%) developed leukemia and 37 (5.41%) developed tumours. At the same time malignant disorders could be observed only in 5 (1.22%) of 406 control animals. In Tables I and II it can be seen that cases of leukemia as well as tumours were of very different origin and structure. According to Table III, malignant processes in the experimental group developed mainly in the animals of the F_4 and F_5 generations.

The DDT content of fatty tissue of the animals in Group 1 and Group 2 was 7.0–11.0 mg/kg and 1.8–2.2 mg/kg respectively.

Discussion. Evaluating our results, it is necessary to mention that in BALB/c mice spontaneous leukemia is unknown. BALB/c mice are, however, susceptible to

[1] *Evaluation of the Toxicity of Pesticide Residues in Food* (FAO-WHO Report, Rome 1964), p. 56.
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chronic pneumonia, and the occurrence of pulmonary tumours has already been described[4]. After having observed our stock-breeding for several years, it was established that chronic pneumonia occurred in 10–15% of the animals and benignant pulmonary adenoma in 5%, whereas the incidence of malignant pulmonary tumours was below 1 ‰.

Table I. Malignant disorders in BALB/c mice

Disorder	Experimental group No. of animals	%	Control group No. of animals	%
Leukemia	24[a]	3.51	1[b]	0.24
Tumour	37	5.41	4	0.98
Total	61	8.92	5	1.22

[a] 7 myeloid, 9 lymphoid and 8 aleucemic leukemia. [b] 1 lymphoid leukemia.

Table II. Type and origin of tumours in BALB/c mice

Type of tumour	No. of animals	Origin
Experimental group		
Adenocarcinoma	11	Rectum (1), small intestine (1), prostate (1), lung (8)
Carcinoma solidum	2	Breast (1), uterus (1)
Carcinoma spinocellulare	1	Cervical dermatoma
Keratinizing squamous cell carcinoma	1	Skin above the thorax
Hepatoma	1	Liver
Angiosarcoma	5	Spleen (1), abdomen (1), cornu uteri (1), subcutaneous connective tissue (2)
Fibromyxosarcoma	1	Subcutaneous connective tissue
Polymorphocellular sarcoma	1	Connecting tissue of the pelvis
Reticulosarcoma	11	Retroperitoneum (2), mediastinum (1), axilla (1), abdomen (1), lymphatic tissue (6)
Non-identified tumour	3	Abdomen (1), subcutaneous connective tissue (1), liver (1)
Total	37	
Control group		
Adenocarcinoma	1	Lung
Carcinoma solidum	1	Breast
Polymorphocellular sarcoma	1	Skin above the thorax
Reticulosarcoma	1	Abdomen
Total	4	

Table III. Distribution of malignant disorders in different generations of BALB/c mice

Generation No.	Age (months)	Experimental group Leukemia	Experimental group Tumour	Control group Leukemia	Control group Tumour
F_1	26	3	2	–	1
F_2	22	2	8	–	–
F_3	18	4	5	–	1
F_4	15	10	10	1	1
F_5	11	5	12	–	1

After chronic oral administration of DDT in amounts smaller than its LD_{50} only mild liver lesions occurred, but essential pathological disorders were not observed either in man[5,6] or in experimental animals[7–10]. Some publications refer to uncertain tumourogenic effects of DDT and DDD administered in large amounts[11–14]. Kelthane, a compound analogous to DDT in mice, caused malformations[15]. According to the available data, after administration of small amounts of DDT (similar to those we mixed with the diet of our experimental group) no blastomogenic effect was ever observed.

The DDT intake of the experimental group being 10 times as much as that of the controls, we suppose that the blastomogenic amount of DDT in BALB/c mice ranges between 0.03–0.05 and 0.3–0.6 mg/kg body weight, and corresponds perhaps to the latter value.

The leukemias and tumours observed showed great polymorphism: 3 types of leukemia and malignant tumours of extremely different localization and structure have been observed. It seems, therefore, that DDT is a universal blastomogenic substance.

When DDT determinations were performed in the tissues of mice, it was noticeable that the accumulated DDT content in the fatty tissue of the experimental group amounted to 7–11 mg/kg. This value was of the same order as the DDT level in the fatty tissue of the urban population[16].

On the basis of present results, however, it seems necessary to point out that small amounts of DDT regularly entering the organism may be injurious to health. Great care therefore seems justified in connection with the use of persistent insecticides like DDT[17].

Zusammenfassung. BALB-c Mäusen wurde während 5 Generationen DDT (0,3–0,6 mg/kg Körpergewicht) verabreicht. Bei 61 Tieren (8,92%) traten maligne Veränderungen ein (Leukemien, Tumoren), während in der Kontrollgruppe nur 5 Tiere (1,22%) erkrankten.

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