been transferred over with the original peritoneal cell suspension as a minor percentage of the initial population, and might have adapted to the culture conditions more rapidly than the macrophage population.

The metabolic activity of cultures of fibroblasts showed little variability over the 1-week-exposure period regardless of the smoke dosage employed. Furthermore, the cultures remained extremely healthy over the period and viability counts relative to controls were much higher than those seen in the corresponding macrophage cultures. Consequently, several experiments were performed in which cultures of fibroblasts being exposed to the highest smoke dosage were maintained for a second week in culture, during which the exposure regime was continued (dosage 2×2).

At the end of the experimental period, these cultures contained more viable cells than corresponding control cultures (130%), and ^{3}H-DNA synthetic rates were elevated up to 8 times those seen in the controls. These data confirm the observations of LEUCHTENBERGER et al.[1,2] employing indirect measures of DNA synthesis, and suggest that cigarette smoke exposure may potentially exert dramatic effects on rates of DNA synthesis in susceptible cells. Direct effects of this nature on nucleic acid synthesis may be involved in the development of hyperplastic changes which are invariably seen in cells lining the respiratory tract of smokers, and may also play a part in the eventual development of neoplasia.

Zusammenfassung. Makrophagen- und Fibroblastenkulturen wurden bis zu 2 Wochen lang frischem Zigarettenrauch exponiert. Während die Makrophagen schon bei geringen Rauchkonzentrationen eine erhöhte Protein- und RNS-Synthese zeigten, wurden bei Fibroblasten keine Veränderungen beobachtet. In höheren Rauchkonzentrationen waren bei den Makrophagen die DNS-Synthesewerte leicht bei den Fibroblasten jedoch stark erhöht.

P. G. HOLT, L. M. ROBERTS and D. KEAST[6]

Department of Microbiology, University of Western Australia, Perth Medical Centre, Shenton Park 6008 (Western Australia), 16 July 1974.

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The Effect of L-Dopa, Noradrenalin and Adrenalin on P-388 Mouse Leukemia, B-16 Mouse Melanoma and E 0771 Mammary Carcinoma

The relationship between levodopa and neoplasia has been discussed by a few authors, contradictory reports having been published as to the effect of the drug upon human and experimental tumors[1–4]. A recurrence of melanoma was reported in 2 patients with Parkinson's disease treated with L-Dopa[5] and a striking temporal relationship was reported between the initiation of L-Dopa therapy and growth of melanoma[4,6]. Levodopa was suspected to enhance tumor growth through an effect of increased growth hormone secretion[7] or by its direct incorporation into melanoma[8]. ROBINSON et al.[1] failed to observe an enhancement of melanoma in L-Dopa treated experimental mice.

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Table I. Effect of L-Dopa, L-Dopa + $CuSO_4$, noradrenalin and adrenalin on the survival time of mice bearing P-388 tumor implanted intraperitoneally

Compound	Dose (mg/kg)	No. of treatments	Route of administration	Mean survival time (days ± S.D.)		Increase[a] or decrease in survival time (%)
				Treated	Controls	
L-Dopa	100	5	i.p.	7.8 ± 0.7	7.9 ± 0.7	0
L-Dopa + $CuSO_4$	100 + 4	5	i.p.	8 ± 1.05	7.9 ± 0.7	0
L-Dopa	150	6	i.p.	7 ± 0.35	8 ± 1.05	13
L-Dopa	250	6	i.p.	7.5 ± 0.4	8 ± 0.7	
L-Dopa	50	9	i.p.	8 ± 0.7	8.5 ± 0.34	6
L-Dopa	50	8	i.p.	9 ± 0.7	9 ± 0.5	0
L-Dopa	50	7	i.p.	9 ± 1.05	9 ± 1	0
Noradrenalin	0.1	5	i.p.	8.2 ± 1.75	7.9 ± 0.7	0.3[a]
Adrenalin	0.1	5	i.p.	7.5 ± 0.7	7.1 ± 0.7	0.7[a]
L-Dopa + $CuSO_4$	100 + 4	5	s.c.	7.2 ± 0.5	7 ± 0.7	0.2[a]
L-Dopa + $CuSO_4$	100	5	i.p.	7.2 ± 0.7	7 ± 1	0.2[a]
	4	5	s.c.			
Noradrenalin	0.1	5	s.c.	8 ± 0.5	7 ± 0.7	14[a]
Adrenalin	0.1	5	s.c.	7.2 ± 0.7	7 ± 0.5	0.2[a]

Table II. Effect of L-Dopa on P-388 tumor implanted intracerebrally

Inoculum (cells/mouse)	Dose (mg/kg)	Route of administration	No. of treatments	Mean survival time (days ± S.D.)		Increase in survival time (%)
				Treated	Controls	
10^6	200	i.p.	3	6.5 ± 0.7	6 ± 0.7	8
10^6	200	per os	5	6.5 ± 1.4	6.5 ± 1.7	0
10^4	200	i.p.	6	10 ± 1.1	10 ± 1.5	0
10^2	200	i.p.	8	11.5 ± 0.7	11 ± 0.35	4

Table III. Effect of L-Dopa on E 0771 mammary carcinoma and B-16 mouse melanoma

Tumor	Dose (mg/kg)	Route of administration	No. of treatments	Mean survival time (days ± S.D.)		Increase in survival time (%)
				Treated	Controls	
E 0771	200	i.p.	8	28 ± 5.1	18 ± 5.6	58
B-16	100	i.p.	9	29 ± 2.4	24 ± 2.7	20
B-16	150	i.p.	9	29 ± 2	24 ± 2.7	20

In an attempt to clarify this subject, a series of experiments was performed to investigate the effect of L-Dopa, noradrenalin and adrenalin on P-388 mouse leukemia, B-16 mouse melanoma and E0771 mouse mammary adenocarcinoma.

Material and methods. The tumors used in this study were P-388, a fast-growing leukemia, and B-16 melanoma, a slow-growing tumor, which are the tumors of choice for testing anti-tumor activity. In addition, the effect upon mouse mammary carcinoma E0771 was also tested. The P-388 tumor was implanted i.p. or intracerebrally (i.c.) at different cell doses beginning with 1×10^2 cells/mouse up to 10^6 cells/mouse. The B-16 mouse melanoma was implanted as 0.1 cm^3 of tumor homogenate i.p. and E0771 mammary carcinoma was implanted s.c. in one piece with a trocar.

The host mice used for the P-388 and B-16 tumors were BDF_1 hybrids or $C_{57}BL_6$ and for the E0771, $C_{57}BL_6$ mice. Each experimental group comprised 10 mice.

The compounds were injected into the tumor-bearing animals 24 h after tumor implantation and injections were repeated every 24 h. The carcinostatic effect was determined according to the Drug Research and Development Instructions[8].

Results and discussion. L-Dopa, adrenalin and noradrenalin did not have any significant effect on the survival time of mice bearing P-388 leukemia transplanted i.p. (Table I) or i.c. (Table II). According to YAMAFUJI et al.[2], L-Dopa, adrenalin and noradrenalin had an inhibitory effect on Sarcoma 180, an effect which was enhanced by copper ions. In our experiments, copper ions did not affect the activity of L-Dopa in P-388 mouse leukemia. A prolongation of the survival time of animals bearing experimental mouse mammary carcinoma E0771 and B-16 melanoma was obtained in L-Dopa treated mice. The effect of L-Dopa on B-16 melanoma was less significant than the clear-cut effect of the drug on mammary carcinoma (Table III).

Studies on the rat pituitary emphasize the fact that dopamine inhibited the release of newly-synthesized prolactin[9]. Prolactin is known to stimulate the growth of breast carcinoma[10]. MINTON and DICKEY[11] suggested that L-Dopa might provide an alternative treatment to steroid therapy in hormone-sensitive cancer. Our findings in experimental mammary carcinoma support this approach.

From our findings it would seem that L-Dopa holds no apparent potential in the treatment of leukemia, nor does it appear to have an enhancing effect upon the growth of melanoma. Its possible usefulness in the treatment of mammary carcinoma, however, should be given further consideration.

Résumé. Le levodopa, l'adrénaline et le noradrénaline administrés à des souris ayant une leucémie P-388, un mélanome B-16, ou un carcinome mammaire E0771 n'ont pas accéléré la croissance de la tumeur ni diminué le temps de survie. L'influence inhibitrice du levodopa fut légère sur le mélanome et très significative sur le E0771.

BATIA SHOHAT, EDNA KOTT and B. BORNSTEIN

Cancer Research Unit, and Department of Neurology, Beilinson Medical Center, Tel Aviv University Medical School, Petah Tikva (Israel), 31 July 1974.

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