gleichen Reiz wie in Figur 1c gehörende Aufzeichnugn (Figur 2) zeigt deutlich die nach Reizbeginn veränderte Atmung in einem verlängerten und danach zwei verkürzten Atemzügen. Im Carotispuls sind in diesem Fall keine sicheren Änderungen nachzuweisen. In anderen stiegen Blutdruck und Pulsfrequenz kurz an um wenige Prozent.

Misst man mit unpolarisierbaren Zn–$ZnSO_4$-Elektroden statt des Hautwiderstandes die zwischen der Innenseite des zweiten und dritten Fingers auftretenden elektrischen Potentialänderungen, so erhält man durchaus entsprechende Befunde. Nach Duftreizen steigt das Potential an um etwa $1 \cdot 10^{-5}$ V und kehrt nach 10–20 sec in die Ruhelage zurück, auch wenn der Reiz länger anhält.

Alle mitgeteilten Erscheinungen sind von äusseren Umständen, z.B. Beunruhigung durch Geräusche, sowie durch Innenfaktoren, z.B. psychischer Erregung und innerer Spannung nach längerer Versuchsdauer, abhängig. In schematischer Deutlichkeit zeigen sie sich nur, wenn die erwähnten Störungen fehlen.

Wie schon frühere Versuche an Gänsen (NEUHAUS[5]), zeigen sich auch beim Menschen die engen Beziehungen zwischen olfaktorischer Perzeption und vegetativem System, was den neuromorphologischen Verhältnissen entspricht. Eine ausführliche Darstellung und Diskussion folgt an anderer Stelle.

Summary. The galvanic skin response in man has been found to be altered by olfactory stimuli. A reduction in skin resistance, which is dependent upon the strength of the stimulus, can be seen after a few seconds, returning to the original level after several minutes. Respiratory rate, blood pressure, and pulse rate are likewise influenced.

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Zoologisches Institut der Universität Erlangen-Nürnberg (Deutschland), 23. Juli 1965.

[5] W. NEUHAUS, *Olfaction and Taste* (Pergamon Press, 1963), p. 111.

Cytotoxicity of Pederin and Some of its Derivatives on Cultured Mammalian Cells

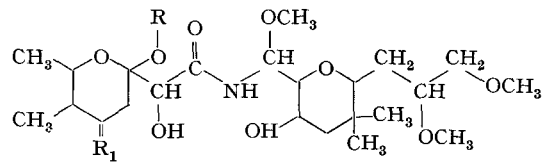
Pederin is a compound obtained in small amounts from *Coleoptera staphylinidae* of the genus *Paederus* (PAVAN and BO[1,2]), whose chemical structure, recently identified by CARDANI et al.[3], is given in Figure 1.

Besides a strong vesicatory action, pederin has some interesting biological properties: very low doses of this compound slow down the growth of tumours induced by chemical agents in *Lupinus albus*, as well as of Sarcoma 180 in the mouse, and cause peculiar chromosomal alterations in the meristem of *Allium coepa* radical apex where the metaphases are arrested before the formation of the spindle (PAVAN[4]).

Pederin and some of its derivatives – pseudopederin, dihydropederin, and dihydropseudopederin[3] (Figure 1) – have been studied on normal cell cultures (mouse embryo and dog kidney cells) and tumoural ones (HeLa and KB strains). These compounds have been employed at different concentrations (from 50 to 0.0001 μg/ml) and for different periods of time (from 1–48 h).

The results obtained on HeLa cells are reported in the Table. Cell cultures treated with these compounds at concentrations of 0.001 μg/ml for 1 or 2 h show an almost complete disappearance of mitosis and particularly the absence of prophases. After 24–48 h of treatment with pederin and its derivatives, a decrease of the growth rate of all the cell cultures tested, inhibition of mitosis, fragmentation of nuclear chromatin in more or less tiny granulations and cytoplasmic alterations (burst, vacuolization) were observed. Nevertheless, near to these cells so severely affected by these agents, a few normal cells can be detected.

Pseudopederin and dihydropseudopederin show an activity and toxicity lower than pederin, being active at doses 10 and 100 times higher (0.01–0.1 μg/ml respectively). The dihydropederin inhibits the mitosis as the pederin does (Figures 4–6) but it is less toxic, determining cytological alterations partially reversible and not as severe as those produced by the same amounts of pederin. The different cellular types have a different sensitivity to



Pederin	$R = CH_3$	$R_1 = CH_2$
Pseudopederin	$R = H$	$R_1 = CH_2$
Dihydropederin	$R = CH_3$	$R_1 = -H, -CH_3$
Dihydropseudopederin	$R = H$	$R_1 = -H, -CH_3$

Fig. 1. Chemical structure of pederin.

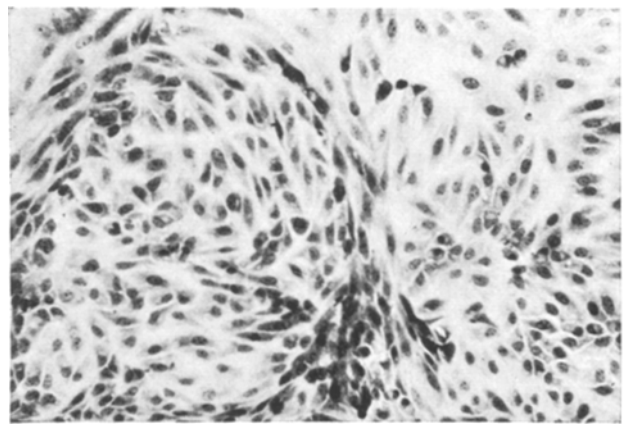


Fig. 2. Dog kidney cell cultures. Control. May-Grümwald-Giemsa. × 100.

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Cytological alterations induced by pederin and some of its derivatives on HeLa cell cultures, after 24 h of treatment

Substances	Doses μg/ml							
	0	0.0001	0.001	0.01	0.1	1	10	50
Pederin	e, h	e, h	b, f	a	a	a	a	i
Pseudopederin	e, h	i	e, h	d, h	c, f	a	a	i
Dihydropederin	e, h	e, h	c, f	a	a	a	a	i
Dihydropseudopederin	e, h	i	e, b	e, b	d, g	d, f	b	a

[a] = complete lysis of cells; [b] = very severe cytological alterations; [c] = severe cytological alterations; [d] = slight cytological alterations; [e] = normal cells; [f] = absence of mitosis; [g] = decrease of mitosis and absence of postmethaphasic stages; [h] = normal mitosis; [i] = not determined.

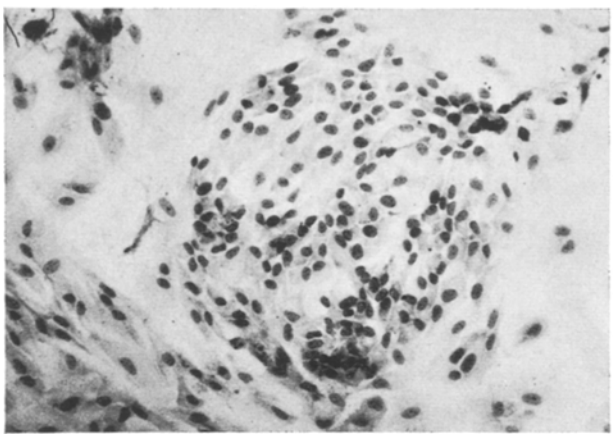

Fig. 3. Dog kidney cell cultures, treated with dihydropederin at dose of 0.0001 μg/ml. May-Grümwald-Giemsa. × 100.

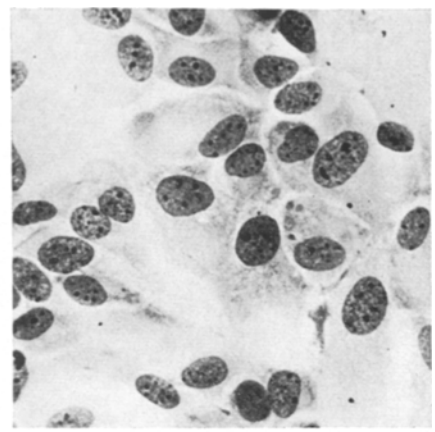

Fig. 5. Dog kidney cell cultures, treated with dihydropederin at dose of 0.0001 μg/ml. May-Grümwald-Giemsa. × 400. Notice the complete absence of mitosis.

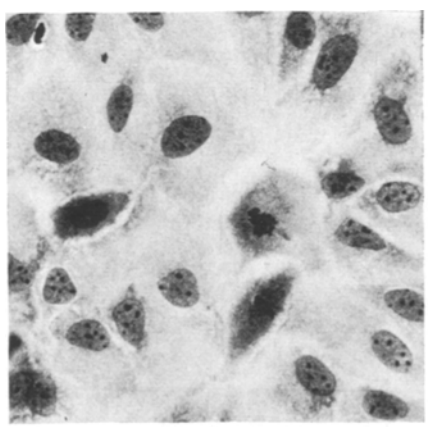

Fig. 4. Dog kidney cell cultures. Control. May-Grümwald-Giemsa. × 400.

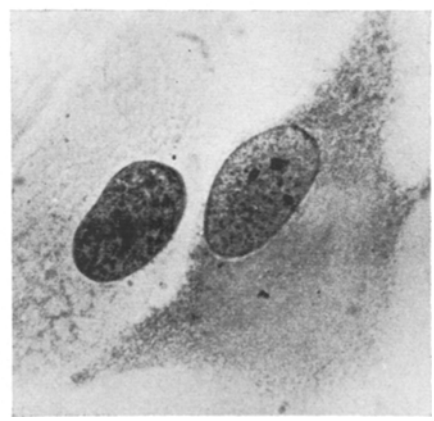

Fig. 6. Dog kidney cell cultures, treated with dihydropederin at dose of 0.0001 μg/ml. May-Grümwald-Giemsa. × 900. Notice the alterations of nuclear chromatin.

the antimitotic action of these compounds. In dog kidney cultures, where fibroblast-like and epithelial cells grow together, the fibroblasts seem to be more sensitive to the action of these agents (Figures 2 and 3).

Pederin concentrations of 0.0001 μg/ml, which are ineffective on mouse embryo and HeLa cells, cause inhibition of mitosis and morphological alterations in dog kidney cell cultures. The mechanism of action of these compounds is not yet known. From the results obtained and previously reported, however, it is possible to conclude that: (1) pederin and its derivatives are very strong mitotic poisons; (2) these agents suppress the entry of cells into prophase; (3) among these compounds dihydropederin seems to be the most interesting one because of

its lower toxicity and partial reversibility of its antimitotic action. Further research could explain the mechanism of action of these antimitotic drugs and suggest the possibility of a chemotherapeutic application.

Riassunto. Studi sulle alterazioni citologiche prodotte dalla pederina e da alcuni suoi derivati su culture di cellule in vitro normali (cellule embrionali di topo, cellule di rene di cane) e tumorali (ceppi HeLa e KB). Queste sostanze determinano, a bassissime concentrazioni, inibizione della crescita delle culture, riduzione fino alla completa scomparsa delle cellule in mitosi e gravi alterazioni citologiche con precoci alterazioni della cromatina nucleare (frammentazione in blocchi o in granuli più o meno fini) e del citoplasma (scoppio, vacuolizzazione, sfrangiamento).

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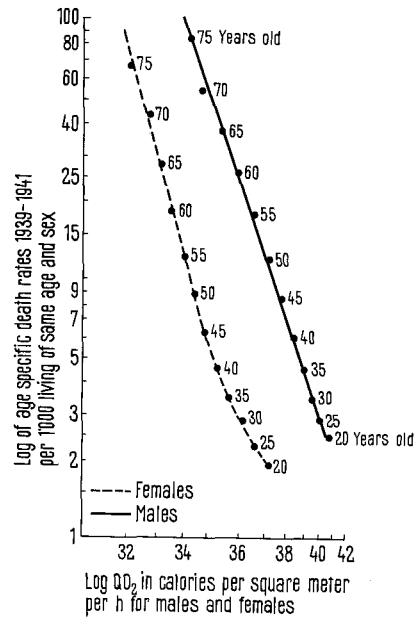
Farmitalia SA, Istituto Ricerche, Milano (Italy), November 10, 1965.

Sex, Lifespan and Smoking

The highly significant correlation between lifespan and body size in mammals[1] implies a relationship to metabolic rate[2] which can be expressed with the dimensional constant ($t_L/kg^{3/4}$), where t_L equals lifespan and $kg^{3/4}$ denotes metabolically active body size[3]. It would follow then that differences in longevity between men and women may be related to their respective metabolic rates. Indeed this already has been illustrated by plotting age-specific death rates of the general population against rate of oxygen consumption – QO_2 per h in calories per m^2 of body surface – separately for men and women at all adult age levels[4]. The two parallel running curves of the plot also reveal that women, in contrast to men, burn at a rate 9–10% lower than their fire of life, a sex difference in metabolic rate corresponding in magnitude to the approximately 9% lower brain weight of women. SACHER has shown that brain weight is an even better predictor of lifespan than body weight, brain weight being correlated about 0.9 with body weight[5]. Another corollary of the relation between metabolic rate and lifespan would be that inherited low metabolic rate favors longer life expectancy. For rats this has been demonstrated by WEISS[6].

The metabolic-rate-dependent difference in lifespan between men and women can be obscured or even reversed by cultural, geographic, economic and other factors. The now excess male mortality – steadily increasing over the last thirty years, as noted by DAVIS[7], ALTMAN and DITTMER[8] and others – was reversed prior to the era of LISTER and SEMMELWEISS. ENTERLINE[9] suggests two kinds of forces at work to account for today's excess male mortality: social, medical, and public health advances have caused rates for certain female diseases, or diseases with low sex mortality ratios (such as tuberculosis, diseases associated with high blood pressure, etc.) to decline, while other factors have brought about increases in male death rates from motor vehicle accidents, lung cancer, and coronary heart diseases. We assert that a constant proportion of the difference is based on the body mass-energy expenditure relation, while deviations due to environmental factors should lend themselves to analysis. An example can be given by replotting on a log-log scale (Figure) the already-mentioned data, depicting the relation between age-specific death rates against oxygen consumption, which were published as a semi-log plot[4]. Only now can it be seen that while the plot illustrating the energy-lifespan relation for females is still a *curved* one, especially for the age group between twenty-five and forty-five, the relation for *males* has become a *straight* line.

Could this log difference be the result of excess male smoking and be related to the steadily increasing excess male mortality? Smoking habits, except for recent years, i.e., since the publishing of official Government reports on a relation between smoking and lung cancer, tend to be



Relation between male and female metabolic rates and death rates (replotted from L. DANZIGER, Dis. nerv. Syst. *10*, 35 (1949) with the permission of the author).

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