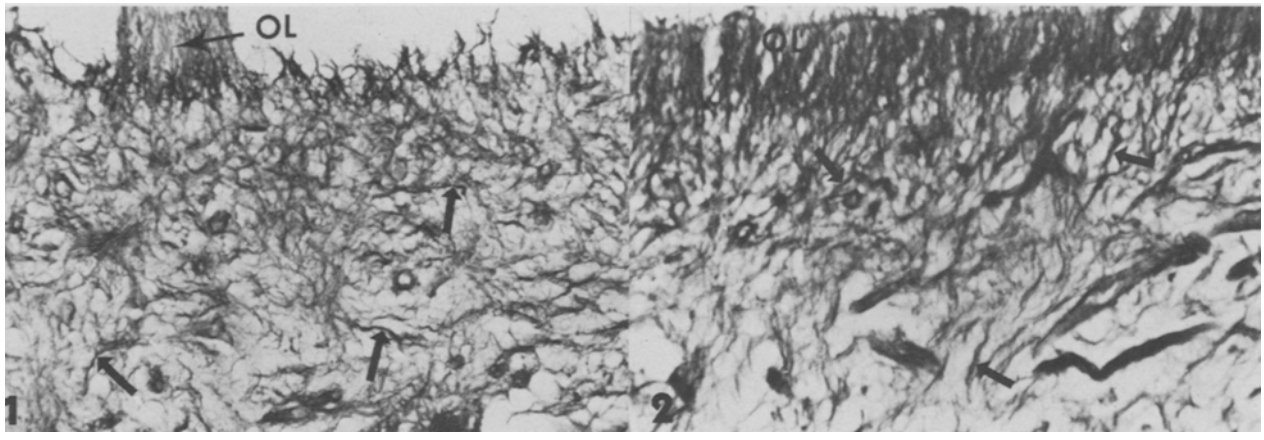

Figures 1 and 2. Human dental pulp. Fig. 1. 12 years old. Fig. 2. 43 years old. – Arrows point to oxytalan fibres in the central part of the pulp. Note penetration of fibres into the odontoblastic layer (OL). Peracetic acid-aldehyde fuchsin. ×270.

fibres in the dental pulp fulfil the light microscopical criteria for oxytalan fibres[2,3]. One may therefore conclude that oxytalan fibres are regular constituents of the intercellular matrix of the human dental pulp in both deciduous and permanent teeth. They very probably represent the light microscopical equivalent of the electron microscopical finding of unstriated 150-Å filaments similar to other microfilaments observed in the supporting tissues of the teeth[8].

The research on oxytalan fibres has been concerned mainly with their distribution and possible functional significance in the periodontal ligament. According to prevailing opinion, their function may be predominantly a mechanical one[2,9]. However, the presence of randomly oriented oxytalan fibres in the mechanically passive connective tissue of the dental pulp can hardly be explained in view of their mechanical role. The presence of oxytalan fibres also in the primitive mucous tissue of the umbilical cord[6], and the clear similarity between oxytalan fibres and invertebrate 'elastic fibres'[10], allow us to suppose that the presence of oxytalan fibres may be related to the primitive nature of the connective tissue in the dental pulp.

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Tumorigenic effect of topical mechlorethamine, BCNU and CCNU in mice

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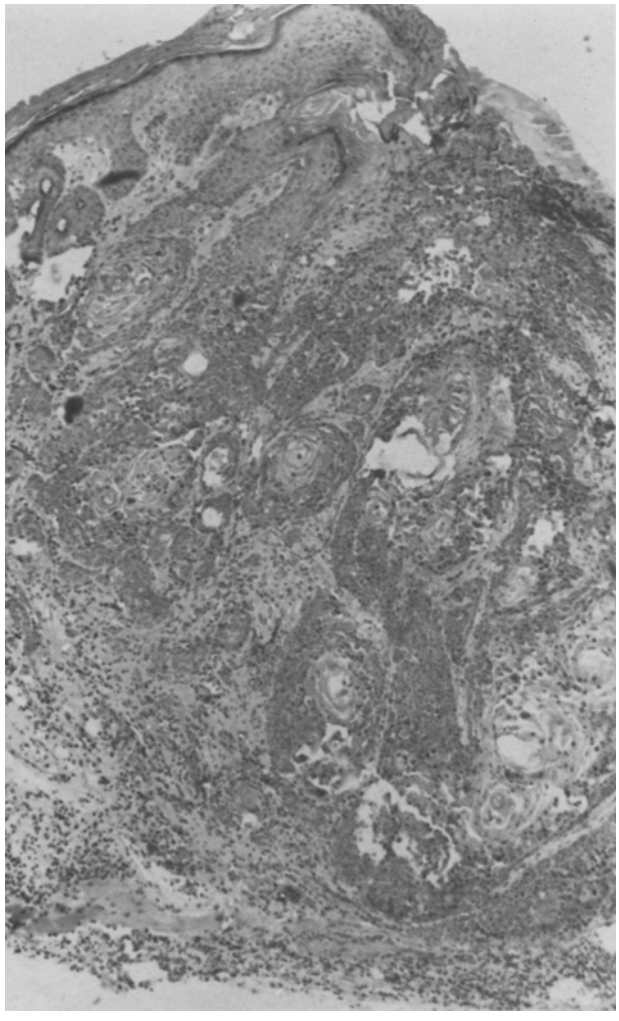
Summary. Mice were painted with mechlorethamine (HN2), carmustine (BCNU) and lomustine (CCNU) for up to 33 weeks. HN2 was a potent carcinogen, producing squamous cell carcinomas in 9 of 33 mice in 1 series. BCNU was a weak carcinogen. CCNU produced no tumors in 1 series.

This study reports the tumorigenic effect of topically applied mechlorethamine (nitrogen mustard, HN2); 1,3-bis-(2-chloroethyl)-1-nitrosourea (carmustine, BCNU); and 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (lomustine, CCNU) in mice.

Although HN2 is carcinogenic when injected s.c.[3] or i.v.[4], in the only report of its topical application[5] painting with HN2 followed by croton oil resulted in warty growths but no carcinomas. BCNU and CCNU are intermediate strength carcinogens when injected in mice and rats[6].

Material and methods. All solutions were made fresh weekly and kept at 4–5 °C. Applications were made to the shaved mid-back of outbred female Swiss mice 8–10 weeks old. Only papillomas at least 1 mm in diameter were counted. All tumors were examined histologically.

Results. Results of series 1, 3 and 4 are summarized in the tables. In series 2 30 mice were painted with 0.1 mg of HN2 or BCNU in 0.2 ml 95% ethanol or with 0.2 ml 95% ethanol alone once weekly for 33 weeks. No tumors occurred in any group. Only a few of the HN2 and none of the BCNU mice



Squamous cell carcinoma in mouse painted with HN2 (series 4).

Table 1. Series 1, mice painted with HN2* and CCNU*

	HN2	(%)	CCNU
Initial number	24		24
At risk for skin tumors**	24		24
Mean survival (days)	140		140
Mice with papillomas only	7		0
Papillomas/affected mouse	2.0		–
Mice with SCC	1		0
Total with skin tumors	8	(33.3)	0

*0.3 mg/0.2 ml 95% ethanol once per week. Observed for 20 weeks. **Surviving at least 97 days (when first papilloma appeared). SCC = squamous cell carcinoma.

Table 2. Series 3, mice painted with HN2* and BCNU*

	HN2	(%)	BCNU
Initial number	30		30
At risk for skin tumors**	29		26
Mean survival (days)	177		176
Mice with papillomas	6	(20.7)	0
Papillomas/affected mouse	1.5		–
Mice with SCC	0		0

*0.1 mg/0.2 ml 95% ethanol 3 times per week. Observed for 26 weeks. **Surviving at least 91 days.

Table 3. Series 4, mice painted with HN2*, BCNU* and EtOH**

	HN2	(%)	BCNU	(%)	EtOH
Initial number	36		48		36
At risk for skin tumors***	33		33		34
Mean survival (days)	214		186		287
Mice with papillomas only	1	(3.0)	1	(4.6)	0
Mice with SCC	9	(27.3)	0		0
Total with skin tumors	10	(30.3)	1	(4.6)	0

*0.1 mg/0.2 ml 95% ethanol 3 times per week. HN2 mice painted for 23 weeks, BCNU mice painted for 29 weeks. Both observed for 34 weeks. **0.2 ml abs. ethanol 3 times per week for 40–42 weeks. Observed for 42 weeks. ***Surviving at least 112 days.

developed a dermatitis. However, at doses of 0.3 mg weekly (series 1) or 0.1 mg 3 times/week (series 3 and 4) irritant dermatitis, alopecia and scarring occurred in a high percentage of the HN2 mice. These did not occur in the BCNU or CCNU mice.

The squamous cell carcinomas in the HN2 mice were mostly infiltrated ulcers 8–25 mm in diameter. They were graded as well differentiated 2 (figure), moderately to poorly differentiated 6, and anaplastic 2. The single papilloma in a BCNU mouse was 5×7 mm and showed premalignant changes.

Discussion. The results indicate that HN2 is a potent topical carcinogen whereas BCNU appears to be a weak topical carcinogen in mice. Although CCNU produced no tumors the number of mice was small.

However, it should be noted that in all series in which HN2 caused tumors there was a high incidence of dermatitis, alopecia and scarring. A non-irritating carcinogenic dose for HN2 was not established. By contrast BCNU and CCNU were non-irritating. Inflammation facilitates percutaneous penetration and this may enhance neoplastic formation.

These findings may have clinical relevance. Mycosis fungoides is commonly treated with HN2. However, Du Vivier et al.[7] found a high incidence of cutaneous malignancies in patients painted for prolonged periods with HN2. These included squamous cell carcinomas in non-exposed areas in 2. Kravitz and McDonald[8] also reported squamous cell carcinomas in 2 patients painted intensively with HN2. One metastasized to the lymph nodes.

Topical BCNU is an effective treatment for mycosis fungoides[9]. Although it often produces irritant dermatitis and telangiectasia the latter has not been accompanied by premalignant changes. Since 1971, 35 patients with mycosis fungoides were treated at UCSF with BCNU and followed for 1 to 8 years. No cutaneous neoplasms in non-exposed areas have been seen.

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