Cancer Chemother Pharmacol (1987) 20: 291–296

Cancer Chemotherapy and Pharmacology

Doxorubicin-induced hair loss in the Angora rabbit: a study of treatments to protect against the hair loss

G. Powis and K. L. Kooistra

Department of Pharmacology, Mayo Clinic & Foundation, Rochester, MN 55905, USA

Summary. An animal model for anticancer drug-induced hair loss has been developed using the Angora rabbit given i.v. doxorubicin, 2 mg/kg, twice weekly for 3 weeks. There was a 167% increase in the weight of hair collected by grooming between weeks 2 and 5, and a 72% inhibition of new hair growth at week 6 compared with non-treated animals. The hairs that grew in the doxorubicin treated rabbits did so at the same rate as in non-treated rabbits and appeared normal by light microscopy. Topical application of dimethylsulfoxide (DMSO), of 10% α-tocopherol in DMSO, of 0.5% naphthazoline hydrochloride in DMSO, of 0.1% fluocinolone acetonide in a propylene glycol base and local hypothermia did not provide any protection against doxorubicin-induced hair loss. Angora rabbits fed an α-tocopherol-deficient diet for 6 weeks showed decreased hair growth compared with animals fed a normal diet or a diet supplemented with 100 mg α-tocopherol acetate twice a week for 6 weeks. Some rabbits fed the α-tocopherol-deficient diet died when given doxorubicin. Rabbits fed the α-tocopherol-supplemented diet showed evidence of protection against doxorubicin-dependent inhibition of new hair growth.

Introduction

A side effect of many anticancer drugs is shedding of hair (effluvium) and hair thinning or baldness (alopecia). Although not life-threatening, the loss of hair can be emotionally devastating for a patient and may lead to a refusal of chemotherapy [25, 33, 39, 42]. Doxorubicin probably causes most problems, and all patients receiving doxorubicin experience some degree of alopecia [3]. Other anticancer drugs that cause alopecia are cyclophosphamide, nitrogen mustard, methotrexate, 5-fluorouracil, vincristine, bleomycin and hydroxyurea [14, 33]. A correlation has been reported between the toxicity of anticancer drugs to bone marrow and damage to hair follicles [10]. There is no standard treatment for anticancer drug-induced alopecia [14, 33].

Human scalp hair grows at about 0.3 mm a day, and the activity of each hair follicle is independent of that of adjacent hair follicles [22]. Between 85% and 95% of scalp follicles are in the growing (anagen) phase whiles 5%–15% are in the non-growing or shedding (telogen) phase. Club hair (non-growing hair with a keratinized club at the base) is retained for about 4 months before being shed. Cytotoxic drugs cause alopecia by injuring the mitotically active anagen follicles and, depending on the degree of injury, hair may be shed within a few days due to excessive constriction of the shaft, or hair growth may continue at a slower rate [16]. There may also be excessive shedding of club hairs (telogen effluvium) [31].

Research into treatments to limit or prevent anticancer drug-induced hair loss has been hampered by the lack of a suitable animal model in which to study the hair loss. Hair growth in most wild animals and nearly all domestic and laboratory animals is synchronous with adjacent hair follicles in the same phase of growth. The animals experience waves of hair growth and periodic moulting, and are inappropriate models for the study of hair growth and drug-induced hair loss that occurs in the human. Among commonly used laboratory animals only guinea pig and Angora rabbit have asynchronous hair growth similar to that in the human [5, 8, 17]. We have used guinea pig and Angora rabbit to study doxorubicin-induced effluvium and alopecia. The Angora rabbit was found to provide the best model in which to study both aspects of hair loss. A number of treatments designed to protect against drug-induced hair loss have been studied.

Materials and methods

Animals. Animals used in the study were Angora rabbits of both sexes, weighing 2.0–3.0 kg (Boomerang Rabbitry, Hector, Minn), and male guinea pigs weighing 300–500 g (Biolab, White Bear Lake, Minn). In an initial study, institutionally bred New Zealand white rabbits of both sexes weighing 1.5–2.5 kg were used. All animals were weighed weekly. Animals were housed individually in stainless steel cages and allowed free access to food and water.

Drugs and treatments. Doxorubicin (Adria Laboratories, Columbus, Ohio) was administered as a 2-mg/ml solution in 0.9% NaCl into the peripheral ear vein of rabbits. An upper dose was chosen based on a report that i.v. doxorubicin at 1 mg/kg twice a week causes mid-dorsal alopecia in the New Zealand white rabbit but is associated with tox-

Offprint requests to: G. Powis, Department of Pharmacology, Mayo Clinic and Foundation, 200 First Street, S. W., Rochester, MN 55905, USA

icity [6]. New Zealand white rabbits received doxorubicin at a dose of 0.25–1 mg/kg (4.4–17.5 mg/m^2) twice a week for 13 weeks, and the Angora rabbits received doxorubicin at a dose of 2 mg/kg (35 mg/m^2) twice a week for 3 weeks. Doxorubicin at the same concentration was administered i.p. to guinea pigs at a dose of 0.12–1 mg/kg (1.3–10.8 mg/m^2) twice a week for 13 weeks.

The treatments used to protect against doxorubicin-induced hair loss in the Angora rabbit were topical application of 5 ml dimethylsulfoxide (Burdick and Jackson, Muskegan, Ohio), 5 ml 0.5% naphthazoline hydrochloride (Ciba Pharmaceutical Co., Summit, NJ) in dimethylsulfoxide, 5 ml 10% α-tocopherol succinate (Sigma Chemical Co., St. Louis, Mo) in dimethylsulfoxide and 2 ml 0.1% fluocinolone acetonide in a base of propylene glycol with citric acid (Synalar Topical Solution, Syntex Laboratory, Palo Alto, Calif). The treatments were applied twice a week to the left flank of the animal 10 min before the administration of doxorubicin. The right flank of the animal was untreated. Animals receiving α-tocopherol succinate in dimethylsulfoxide were washed with shampoo 24 h later to prevent matting of the hair by excess α-tocopherol succinate and dried with warm air. The skin on the left flank of some animals was shaved and sensitized [20] by treatment with 5 ml 2% 2,4-dinitrochlorobenzene (Sigma Chemical Co., St. Louis, Mo) in acetone 1 week before the first dose of doxorubicin. The same area was treated with 5 ml 0.1% 2,4-dinitrochlorobenzene in acetone by topical application at weekly intervals.

Local hypothermia was achieved using a 10 × 15 cm pack of Blue Ice Gel (Divajex, Tustin, Calif) held in place against the left flank of the animal with an adjustable wrap for 2 h, commencing 15 min before administration of doxorubicin. The ice pack was kept in a freezer at −20° C until use. Some Angora rabbits were fed an α-tocopherol-deficient diet (ICN Nutritional Biochemicals, Cleveland, Ohio), while other rabbits were given 100 mg (136 IU) α-tocopherol acetate (Sigma Chemical Co.) by mouth twice a week for 6 weeks before, and during the study. α-Tocopherol in plasma was measured by the method of Jansson et al. [21].

Hair growth in the New Zealand white rabbit was measured by shaving the flanks of each animal with an electric hair clipper at the start of the study and then shaving a 4 × 6 cm patch on either flank at 13 weeks and weighing the hair. Hair growth in the Angora rabbit was measured by shaving the flanks of the animal at the beginning of the study and then shaving a new 4 × 6 cm patch on either flank of the animal at weekly intervals and weighing the hair. In animals receiving topical treatments the weight of hair collected from the untreated right flank acted as the control for hair collected from the treated left flank. In addition, every week 20 hairs were epilated with forceps from four different sites between the shaved patches on both flanks of the animal. The length of the epilated hairs was measured with calipers and the hairs were examined under a light microscope. Angora rabbits were groomed weekly as part of their normal care. Grooming was performed in a consistent manner using a bristle brush with each non-shaved area of the animal receiving ten strokes of the brush. The hair gathered on the brush was collected and weighed.

Groups of results were analyzed for statistical significance using Student's *t*-test [34].

Results

Guinea pig

Attempts to produce inhibition of hair growth with doxorubicin in the guinea pig were unsuccessful. Although there was thinning of the hair in some animals at the highest dose of doxorubicin, the effect was not consistent and most animals died without signs of hair loss. The median survival of groups of four guinea pigs receiving twice-weekly i.p. injections of doxorubicin at 0.12 mg/kg was 85 days, at 0.25 mg/kg 60 days, at 0.5 mg/kg 32 days, and at 1 mg/kg 16 days.

New Zealand white rabbits

Doxorubicin was administered to groups of three New Zealand white rabbits at doses of 0.25, 0.5 and 1 mg/kg twice a week for 13 weeks. At each of the 0.5 and 1 mg/kg dose levels one of the three animals died. The increase in weight of the surviving animals over 13 weeks was 87%, 50% and 37% at doxorubicin doses of 0.25, 0.5 and 1 mg/kg, and 82% in non-treated animals. There was noticeable thinning of the hair in rabbits receiving 1 mg doxorubicin/kg, particularly on the dorsal surface. This has previously been reported to be a sensitive area for doxorubicin-induced hair loss in this strain of rabbit [6]. The mean weight of hair that had grown on a 4 × 6 cm patch on either flank of the animal at the end of 13 weeks was 1.61, 1.53 and 0.38 g at doses of doxorubicin of 0.25, 0.5 and 1 mg/kg, and 1.45 g in non-treated animals. The new hair growth was patchy and the amount of hair collected depended very much on the area shaved. For this reason the New Zealand white rabbit is not a good model for the quantitative study of doxorubicin-induced hair loss.

Angora rabbit

Preliminary studies showed that doxorubicin at 2 mg/kg twice a week for 3 weeks was well tolerated by Angora rabbits with no lethality. The normal gain in body weight was inhibited by the doxorubicin treatment, but there was no loss of body weight (Fig. 1) and the animals appeared healthy. Noticeable thinning of the hair started a few weeks after doxorubicin treatment, together with shedding of hair in the cage.

Different methods for measuring hair growth and effluvium were studied. The length of epilated hairs increased at the same rate in non-treated and doxorubicin-treated rabbits (Fig. 2). Thus, although new hair growth in doxorubicin-treated animals was less than in control animals, the hairs that grew did so at the same rate as in control animals. When the epilated hairs were examined by light microscopy there were no histological changes that could be consistently ascribed to the administration of doxorubicin. There was no decrease in the diameter of the hair bulb or keratogenous zone, and no measurable constriction of the distal hair shaft, which has been reported in hair of humans receiving cytotoxic drugs [10].

There was a significant decrease in the weight of hair collected by shaving a 4 × 6 cm patch on the flanks of Angora rabbits given doxorubicin compared with that collected in the same way from non-treated rabbits (Fig. 3). There was a maximum 72% inhibition of new hair growth at 6 weeks. Angora rabbits treated with doxorubicin shed more hair on grooming than untreated rabbits (Fig. 4). The ef-

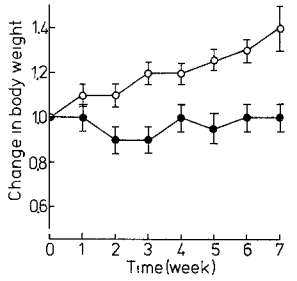

Fig. 1. The Change in body weight of Angora rabbits produced by doxorubicin. ○, Untreated rabbits; ●, rabbits receiving doxorubicin, 2 mg/kg, i.v. twice a week for the first 3 weeks. Values are means ± SE of four animals and are shown normalized to initial body weight (untreated 2.4±0.1 kg; doxorubicin-treated 2.5±0.1 kg)

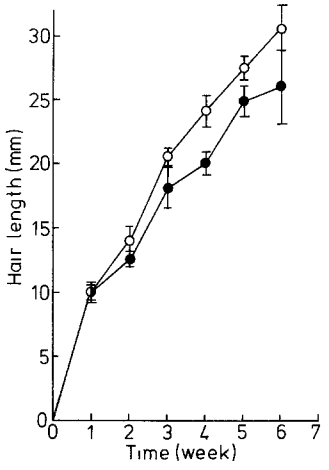

Fig. 2. Effect of doxorubicin on hair length in the Angora rabbit. ○, Untreated rabbits; ●, rabbits given doxorubicin, 2 mg/kg, i.v. twice a week for the first 3 weeks. Animals were shaved at the start of the study and the length of 40 hairs epilated from both flanks of the animal was measured at weekly intervals. Values are means ± SE from four animals

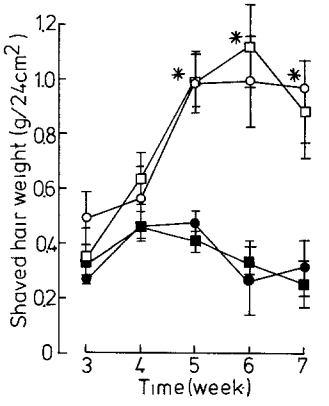

Fig. 3. Effect of doxorubicin on hair growth in the Angora rabbit. Both flanks of the animal were shaved at the start of the study. Hair was then shaved from a new patch 4×6 cm in area on either flank of the animal at weekly intervals and weighed. ○ Left, □, right flank of treated rabbits; ● left and, ■ right flank of rabbits given doxorubicin, 2 mg/kg, i.v. twice a week for the first 3 weeks. Values are means ±SE from four animals. *$P < 0.05$ for the combined values of both flanks of non-treated animals compared with doxorubicin-treated animals

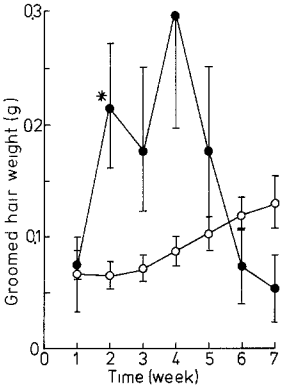

Fig. 4. Effect of doxorubicin on shed hair weight in the Angora rabbit. ○, Non-treated rabbits; ● rabbits given doxorubicin, 2 mg/kg, i.v. twice a week for the first 3 weeks. Values are means ± SE from four animals. Shed hair was collected by grooming the animals at weekly intervals and weighed. *$P < 0.05$ compared with the non-treated value

fect was significant only at week 2 and the amount of hair collected had returned to control values by week 6.

Prevention of doxorubicin-induced hair loss

The effect of a number of topical treatments on doxorubicin-induced inhibition of new hair growth was studied in Angora rabbits 5 weeks after the start of doxorubicin administration (Table 1). Each animal served as its own control, new hair growth on the treated left flank being compared with new hair growth on the non-treated right flank. Effluvium was also measured as the cumulative weight of hair collected by grooming between weeks 2 and 5. The topical treatments studied were dimethylsulfoxide, dimethylsulfoxide containing 10% α-tocopherol, dimethylsulfoxide containing 0.5% naphthazoline hydrochloride, 0.1% fluocinolone acetonide in a propylene glycol base, 2,4-dinitrochlorobenzene skin sensitization, and local hypothermia. 2,4-Dinitrochlorobenzene treatment was lethal, all the animals dying the week after the first sensitization with 0.1% 2,4-dinitrochlorobenzene. Whether this represents a direct toxicity of the treatment to Angora rabbits or an interaction with doxorubicin is not clear, since no rabbits were given 2,4-dinitrochlorobenzene alone.

None of the topical treatments offered significant protection against doxorubicin-induced inhibition of new hair growth. Dimethylsulfoxide treatment and hypothermia significantly inhibited new hair growth on both the treated and the non-treated flanks of the animals. This may be a stress response to the treatment. None of the topical treatments protected against doxorubicin-induced effluvium. This is not surprising, since hair loss was measured over the entire body and not just the treated area.

The effects of an α-tocopherol-deficient diet and an α-tocopherol-supplemented diet on inhibition of new hair growth by doxorubicin in the Angora rabbit are shown in Table 2. α-Tocopherol deficiency itself led to a 58% decrease in new hair growth compared to animals fed a normal diet. An α-tocopherol-supplemented diet did not stimulate new hair growth more than a normal diet. When doxorubicin was administered to rabbits receiving an α-tocopherol-deficient diet two of the three animals died within 3 weeks and no accurate assessment of the effect of α-toco-

Table 1. Effect of topical treatments on doxorubicin-induced effluvium and inhibition of hair growth in the Angora rabbit
Doxorubicin, 2 mg/kg, was administered to Angora rabbits i.v. twice a week for 3 weeks. Treatments were applied to the left flank of the animal at the same time as doxorubicin. The untreated right flank acted as a control. DMSO is dimethylsulfoxide. Local hypothermia employed an ice pack held against the left side of the animal for 2 h. *n*, number of animals surviving at 5 weeks/original number of animals. Groomed hair weight is the cumulative weight of hair collected by weekly grooming between weeks 2 and 5. Shaved hair weight is the weight of hair collected by shaving a 4 × 6 cm patch on either flank of the animal at week 5. Values are means ± SE

Treatment	*n*	Body weight at week 5 as % of initial weight	Groomed hair weight mg	Shaved hair weight	
				Non-treated right flank mg/24 cm²	Treated left flank mg/24 cm²
Control	4/4	126.1 ± 3.9**	80 ± 9**	988 ± 109**	1042 ± 101**
Doxorubicin					
No treatment	3/3	95.8 ± 2.6*	214 ± 71*	486 ± 31*	411 ± 46*
DMSO	3/3	94.6 ± 20.1	268 ± 109*	310 ± 8*,**	215 ± 50*,**
DMSO/10% α-tocopherol	3/3	90.6 ± 4.3*	178 ± 38*	476 ± 159*	262 ± 250*
DMSO/0.5% naphthazoline	3/5	98.0 ± 17.0	117 ± 53	474 ± 42*	550 ± 25*
2,4-Dinitrochlorobenzene	0/3	–	–	–	–
0.1% Fluocinolone acetonide	3/3	100.6 ± 19.4	ND	453 ± 57*	262 ± 41*
Hypothermia	3/3	93.7 ± 8.2*	157 ± 60	153 ± 56*,**	133 ± 47*,**

* $P < 0.05$ for compared to the appropriate treated non-doxorubicin control value; ** $P < 0.05$ compared to the value in doxorubicin-treated animals. None of the treatments produced a significant difference in the values for the treated and the non-treated flanks of the animal
ND, not determined because of matting of the hair over the treated area

Table 2. Effect of dietary α-tocopherol on doxorubicin-induced inhibition of hair growth in the Angora rabbit
Angora rabbits were fed either a normal diet or an α-tocopherol-deficient diet, or were given oral α-tocopherol acetate 100 mg/kg twice a week for 6 weeks before and then during the study. Doxorubicin, 2 mg/kg, was administered twice a week for 3 weeks. Hair growth was measured as the mean weight of hair collected by shaving 4 × 6 cm patches on both flanks of the animal 5 weeks after doxorubicin administration. *n*, number of animals surviving at week 5 after doxorubicin/original number of animals. Values are mean ± SE

Treatment	*n*	Body weight at week 5 (% of initial weight)	Shaved hair weight mg/24 cm²
Control			
Normal diet	3/3	119.5 ± 9.6	841 ± 40
α-Tocopherol-deficient diet	3/3	139.2 ± 7.0	357 ± 11*
α-Tocopherol-supplemented diet	3/3	133.0 ± 3.4	745 ± 85
Doxorubicin			
Normal diet	3/3	87.5 ± 11.2*	311 ± 117*
α-Tocopherol-deficient diet	1/3	75.4	468
α-Tocopherol-supplemented diet	3/3	82.2 ± 15.7*	745 ± 70

* $P < 0.05$ compared with the value in non-doxorubicin-treated animals receiving a normal diet

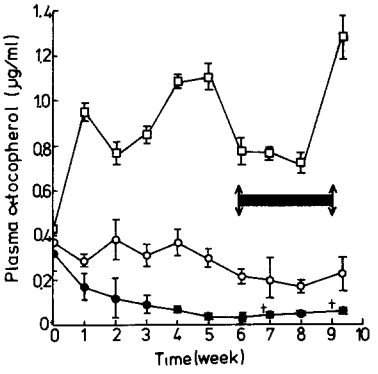

Fig. 5. The effect of dietary modification on plasma α-tocopherol levels in Angora rabbits. ○, Control rabbits; ●, rabbits fed a α-tocopherol-deficient diet, and □ rabbits receiving 100 mg α-tocopherol acetate p.o. twice a week. Values are means ± SE from three animals. Doxorubicin treatment was given in weeks 6–9 (*bar*). † animals dying

pherol deficiency on doxorubicin inhibition of new hair growth could be made. An α-tocopherol supplemented diet completely prevented the inhibition of new hair growth by doxorubicin. To confirm that the dietary modification produced changes in the α-tocopherol status of the animals plasma α-tocopherol concentrations were measured at weekly intervals (Fig. 5). The α-tocopherol deficient diet produced an 85% decrease and the α-tocopherol supplemented diet a 258% increase in the plasma concentration of α-tocopherol at 6 weeks.

Discussion

Doxorubicin was chosen as the drug with which to study loss of hair because large numbers of patients receive doxorubicin and it has been reported to cause some degree of hair loss in all patients who receive the drug [3]. A loss of hair produced by cytotoxic drugs in the human can result from a combination of mechanisms [10]. Severe damage to

the hair follicle can lead to complete cessation of hair growth and the loss of existing hairs with a necrotic anagen sheath adhering to them (true anagen effluvium). If the damage is less severe or of brief duration the hair continues to grow but with a weak and constricted area in the shaft. When this constriction grows above the follicular orifice the hair breaks with minor trauma, producing hair shedding.

The guinea pig exhibits asynchronous hair growth similar to that in the human [8] and has been used to study problems pertaining to loss of hair in the human caused by infection and hormonal disturbances [5], although not loss of hair due to cytotoxic chemicals. We found that the guinea pig was unsuitable for the study of doxorubicin-induced loss of hair because of the sensitivity of the guinea pig compared with other species to the lethal effects of chronic doxorubicin administration [18]. There have been reports of effluvium and inhibition of hair growth caused by chronic doxorubicin administration in New Zealand white rabbits, but only at doses of doxorubicin producing lethality in 40%–50% of the animals [4, 6]. We saw effluvium and inhibition of new hair growth in New Zealand white rabbits administered close to lethal doses of doxorubicin. The effect was difficult to quantify because of the synchronous nature of hair growth in the New Zealand white rabbit with the new hair growing in irregular patches [9]. Because of these problems the New Zealand white rabbit is a poor model with which to study the loss of hair caused by doxorubicin.

The Angora rabbit, unlike other breeds of rabbit, shows asynchronous hair growth [7, 17]. A single gene controls the continued growth of hair at a normal rate all over the body and the hair becomes several times longer than normal. We found the Angora rabbit was a good model for studying effluvium and inhibition of new hair growth caused by doxorubicin. Doxorubicin, 2 mg/kg, i.v. twice a week for 3 weeks produced a 72% inhibition of new hair growth at week 6 and a 167% increase in hair collected by grooming between weeks 2 and 5. The hairs that grew on the doxorubicin-treated rabbits did so at the same rate as on non-treated animals and appeared histologically normal. The lack of histological changes may reflect the way in which doxorubicin was administered, as several closely spaced injections that does not produce a well-defined constriction of the distal hair shaft, as has been reported in the hair of humans receiving cytotoxic drugs [10]. It is noteworthy that another anticancer drug, cyclophosphamide, has been used commercially to depilate Angora rabbits for collection of their wool [32].

A number of topical treatments were studied for their ability to prevent inhibition of hair growth by doxorubicin, but all were found to be ineffective. The treatments were; dimethylsulfoxide, which applied topically decreases skin necrosis caused by s.c. infiltration of doxorubicin in the rat, pig and human [13, 29]; 10% α-tocopherol succinate in dimethylsulfoxide, which applied topically also decreases doxorubicin-induced skin necrosis in the rat and guinea pig [27, 36]; 0.5% naphthazoline hydrochloride, a vasoconstrictor which applied to skin dissolved in dimethylsulfoxide causes local vasoconstriction [35] and might, therefore, limit delivery of doxorubicin to the hair follicles; and 0.1% fluocinolone acetonide in a propylene glycol base, a synthetic corticosteroid that causes hypertrichosis [15]. Topical 2,4-dinitrochlorobenzene has been used as an immunostimulant to treat alopecia areata in the human [20], but under the conditions used in rabbit it was lethal. Scalp hypothermia employing ice packs, cooled water and refrigerated air to produce local vasoconstriction and decreased delivery of doxorubicin to the hair follicles has been used in attempts to prevent doxorubicin-induced alopecia in cancer patients, with varying degress of success [2, 11, 12, 19, 37, 41]. The technique can only be used in patients who are not at risk of developing subsequent scalp metastases and, thus, excludes patients with leukemia and multiple myeloma [33]. In the Angora rabbit we found that local hypothermia did not prevent doxorubicin-induced inhibition of hair growth. The treatment itself produced inhibition of hair growth in areas not exposed to the hypothermia, perhaps as a response to the stress of the treatment.

The only treatment tested which provided protection against doxorubicin-induced inhibition of hair growth in the Angora rabbit was dietary α-tocopherol. Topical α-tocopherol has been reported to stimulate hair growth in the rabbit [1] but, as previously noted, we found that applied in dimethylsulfoxide it did not protect against doxorubicin-induced inhibition of hair growth. α-Tocopherol is a free radical scavenger and has been reported to protect rabbits against the acute cardiotoxicity of doxorubicin [38], which is thought to be a free radical-mediated process [28], without affecting the antitumor activity of doxorubicin [26]. While promising, the protection offered by dietary α-tocopherol against doxorubicin-induced inhibition of hair growth in the Angora rabbit may not extend to the human. Clinical trials of α-tocopherol have shown no protection of patients against doxorubicin cardiotoxicity [23, 40]. In one of these studies Legha et al. [23] reported that α-tocopherol did not protect patients against doxorubicin-induced alopecia, although the patients also received cyclophosphamide which causes alopecia by a mechanism that does not involve free radicals [14]. A preliminary report by Wood [42] indicated that large doses of oral α-tocopherol may protect patients against doxorubicin-induced alopecia. Based on this report, studies were conducted by Perez et al. [30] and Martin-Jimenez et al. [24] on the ability of large doses of oral α-tocopherol to protect patients against doxorubicin-induced alopecia. No protection was found in either study. However, the patients received other cytotoxic drugs in combination with doxorubicin, including cyclophosphamide, 5-fluorouracil, vincristine and cisplatin. It is possible that these drugs cause alopecia by a mechanism that is not affected by α-tocopherol.

In summary, an animal model for doxorubicin-induced effluvium and inhibition of hair growth such as occurs in cancer patients has been developed using the Angora rabbit and a 3-week treatment with doxorubicin. Topical treatment of the rabbits with a number of drugs or local hypothermia gave no protection against the hair loss. Supplementation of the diet with α-tocopherol completely prevented doxorubicin-dependent inhibition of hair growth.

Acknowledgements. We wish to thank Dr Bruce Svingen for measurement of plasma α-tocopherol concentrations. We thank Dr Mark Pittelkow for his helpful suggestions. The excellent secretarial assistance of Ms Wanda Rhodes is gratefully acknowledged.

References

1. Akhtar MS, Jabbar MA (1981) Effect of topical application of oils of amla, coconut, sarson and samsol on growth of rabbit's hair and sheep wool. J Punjab Med Assoc 31: 246
2. Anderson JE, Hunt JM, Smith IE (1981) Prevention of doxorubicin-induced alopecia by scalp cooling in patients with advanced breast cancer. Br Med J 282: 423
3. Benjamin RS (1975) A practical approach to adriamycin (NSC-123127) toxicology. Cancer Chemother Rep [III] 6: 191
4. Bertazzoli C, Chieli T, Ferni G, Ricevuti G, Solcia E (1972) Chronic toxicity of adriamycin: A new antineoplastic agent. Toxicol Appl Pharmacol 21: 287
5. Bosse K (1965) Growth and replacement of hair in the guinea pig: In: Rook AJ, Walton GS (eds) Comparative physiology and pathology of the skin. Davis, Philadelphia, p 151
6. Breed JGS, Zimmerman AME, Dormans JAMA, Pinedo HM (1980) Failure of the antioxidant vitamin E to protect against adriamycin-induced cardiotoxicity in rabbit. Cancer Res 40: 2033
7. Castle WE (1903) The heredity of "angora" coat in mammals. Science 18: 760
8. Castle WE, Forbes A (1906) Heredity of hair length in guinea pigs and its bearing on the theory of pure gametes. Carnegie Inst Wash Publ 49: 5
9. Crary DD, Sawin PB (1953) Some factors influencing the growth potential of the skin in the domestic rabbit. J Exp Zool 124: 31
10. Crounse RG, Van Scott EJ (1960) Changes in scalp hair roots as a measure of toxicity from cancer chemotherapeutic drugs. J Invest Dermatol 35: 83
11. Dean JC, Salmon SE, Griffiths KS (1979) Prevention of doxorubicin-induced hair loss with scalp hypothermia. N Engl J Med 301: 1427
12. Dean JC, Griffith KS, Cetals TC (1983) Scalp hypothermia: a comparison of ice packs and the kold kap in the prevention of doxorubicin-induced alopecia. J Clin Oncol 1: 33
13. Desai MH, Teres D (1981) Prevention of doxorubicin-induced skin ulcers in the rat and pig with dimethylsulfoxide. Cancer Treat Rep 66: 1371
14. Dunagin WG (1982) Clinical toxicity of chemotherapeutic agents: dermatologic toxicity. Semin Oncol 9: 14
15. Ebling FJ, Rook A (1972) Hair: In: Rook A, Wilkinson DS, Ebling FJG (eds) Textbook of dermatology, vol 2. Blackwell, Oxford, p 1559
16. Flesch P (1963) Inhibition of keratinizing structures by systemic drugs. Pharmacol Rev 15: 653
17. Fraser AS (1952) A note on the growth of the Rex Angora coats. J Genet 51: 237
18. Fujita K, Shinpo K, Yamada K, Sato T, Niimi H, Shamoto M, Nagatsu T, Takeuchi T, Umezawa H (1982) Reduction of adriamycin toxicity by ascorbate in mice and guinea pigs. Cancer Res 42: 309
19. Guy R, Parker H, Shah S, Geddes D (1982) Scalp cooling by thermocirculator. Lancet I: 937
20. Happle R, Echternacht K (1977) Induction of hair growth in alopecia areata with DCNB. Lancet II: 1002
21. Jansson L, Nilsson B, Lindgren R (1980) Quantitation of serum tocopherols by high-performance liquid chromatography with fluorescence detection. J Chromatogr 181: 242
22. Kligman AM (1959) The human hair cycle. J Inv Dermatol 33: 307
23. Legha SS, Wang YM, Mackay B, Ewer M, Hortobagy GN, Benjamin RS, Ali MK (1982) Clinical and pharmacologic investigation of the effects of α-tocopherol on adriamycin cardiotoxicity. Ann NY Acad Sci 393: 411
24. Martin-Jimenez M, Diaz-Rubio E, Gonzalez Larriba JL, Sangro B (1986) Failure of high-dose tocopherol to prevent alopecia induced by doxorubicin. N Engl J Med 315: 894
25. Maxwell MB (1980) Scalp tourniquets for chemotherapy-induced alopecia. Am J Nursing 80: 900
26. Myers CE, McGuire WP, Liss RH, Ifrim I, Grotzinger K, Young RC (1977) Adriamycin: the role of lipid peroxidation in cardiac toxicity and tumor response. Science 197: 165
27. Nobbs P, Barr RD (1983) Soft tissue injury caused by antineoplastic drugs is inhibited by topical dimethylsulfoxide and alpha-tocopherol. Br J Cancer 48: 873
28. Nohl H, Jordan W (1983) OH-generation by adriamycin semiquinone and H_2O_2; an explanation for the cardiotoxicity of anthracycline antibiotics. Biochem Biophys Res Commun 114: 197
29. Olver IM, Schwartz MA (1982) Use of dimethylsulfoxide in limiting tissue damage caused by extravasation of doxorubicin. Cancer Treat Rep 67: 407
30. Perez JE, Macchiavelli M, Leone BA, Romero A, Rabinovich MG, Goldar D, Vallejo C (1986) High-dose alpha-tocopherol as a preventive of doxorubicin-induced alopecia. Cancer Treat Rep 70: 1213
31. Rook A (1965) Abnormal hair growth in man: In: Rook AJ, Walton GS (eds) Comparative physiology and pathology of the skin. Davis, Philadelphia, p 231
32. Rougeot J, Thebault RG (1970) Utilisation de la cyclophosphamide comme substance depilatoire pour la recolte des poiles du lapin angora. Ann Zootech 19: 229
33. Seipp CA (1985) Adverse effects of treatment-hair loss. In: De Vita VT, Hellman S, Rosenberg SA (eds) Cancer, principle and practice of oncology, 2nd edn. Lippincot, Philadelphia, p 2007
34. Snedecor GW, Cochran WC (1967) Statistical methods. Iowa State University Press, Ames Iowa, p 91
35. Stoughton RB, Fritsch W (1964) Influence of dimethylsulfoxide (DMSO) on human percutaneous absorption. Arch Dermatol 90: 512
36. Svingen BA, Powis G, Appel PL, Scott M (1981) Protection against adriamycin-induced skin necrosis in the rat by dimethylsulfoxide and α-tocopherol. Cancer Res 41: 3395
37. Symonds RP, McCormick CV, Maxted KJ (1986) Adriamycin alopecia prevented by cold air scalp cooling. Am J Clin Oncol 9: 454
38. Wang YM, Madanat FF, Kimball JC, Gleiser CA, Ali MK, Kaufman MW, van Eys J (1980) Effect of vitamin E against adriamycin-induced toxicity in rabbits. Cancer Res 40: 1022
39. Welch D, Lewis K (1980) Alopecia and chemotherapy. Am J Nursing 80: 903
40. Wertzman SA, Lorell B, Carey RW, Kaufman S, Stossel TP (1980) Prospective study of tocopherol prophylaxis for anthracycline toxicity. Current Ther Res 28: 682
41. Wheelock JB, Myers MB, Krebs HB, Goplerud DR (1984) Ineffectiveness of scalp hypothermia in the prevention of alopecia in patients treated with doxorubicin and cisplatin combinations. Cancer Treat Rep 68: 1387
42. Wood LA (1985) Possible prevention of adriamycin-induced alopecia by tocopherol. N Engl J Med 312: 1060

Received March 4, 1987/Accepted July 15, 1987