DRUGS EXPTL. CLIN. RES. **XXI**(5) 199–206 (1995)

POSSIBILITIES OF SCAR TREATMENT AFTER THORACIC SURGERY

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Summary: *During a ten year observation period it was found that scar formation after thoracic surgery is influenced by various factors: metabolism, operative technique and factors of a general nature. On the basis of these findings, a study was carried out to investigate the effect of the scar-specific Contractubex gel (Merz + Co., D-Frankfurt/Main), containing 10% onion extract, 50 U sodium heparin per g of gel and 1% allantoin, in the treatment of children who underwent thoracic surgery and to evaluate its effect on scar development. Before and during the six-month treatment period, both macromorphology and scar colour were assessed; furthermore, a global evaluation of the therapeutic result was made. Additionally, the scars were characterized after a six-month treatment-free follow-up period. The results of 38 Contractubex-treated and 27 untreated patients were compared. In the treated scars, the global evaluation of the therapeutic result was better than in the untreated scars. In the Contractubex group, the rating was "good" and "very good" in 84% of cases, as compared to 59% of the untreated cases. In the treated group, the increase in scar size was markedly lower than in the untreated patients. The treated scars showed a tendency towards quicker paling than the untreated scars. In the treated group, the conversion of primary physiological scars to unphysiological scars (hypertrophic or keloidal scars) was less frequent than in the untreated group. The tolerability of the product was very good in 37 of the 38 treated patients, and good in one patient. All scar-specific effects of Contractubex continued to persist after the end of treatment.*

Introduction

The frequency of unphysiological scars occurring in children in the area of the operation site on the chest was investigated and documented over a period of ten years. It was found (unpublished results) that the following parameters play an important part in scar development:
age of the child,
localization of the wound,
tension in the wound area,
surgery in a primarily infected area,
suture technique, especially the subcutaneous and the intracutaneous suture techniques,
application of relieving Steristrips.
normal protein balance,
anabolic or catabolic conditions of metabolism,

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0378-6501/95/00201 + 8 $02.00/0

time of removing the stitches,
extent and duration of wound oedema,
surgery in traumatized tissue,
wound ischaemia caused by strong tension in the wound area,
incision's orientation to the lines of relaxed skin tension,
serum levels of zinc and magnesium,
normal clotting factor XIII.

Investigations in 2,500 children revealed an influence on scar development if the total protein level was reduced by more than 50% in conditions of catabolic metabolism lasting longer than one week and if the amount of clotting factor XIII was reduced by more than 50% (Fig. 1).

Increased tension on the wound and wound ischaemia as a result of tension on the wound margins had a promoting effect on the formation of hypertrophic scars. 30% and 80% of such patients had hypertrophic scars. Additional factors that were responsible for the development of a hypertrophic scar were pre-operatively infected wounds, postoperative wound oedema and postoperative infections in the wound area, as well as sutures applied to traumatized tissue (Tables Ia and Ib).

Depending on the influence of the above-men-

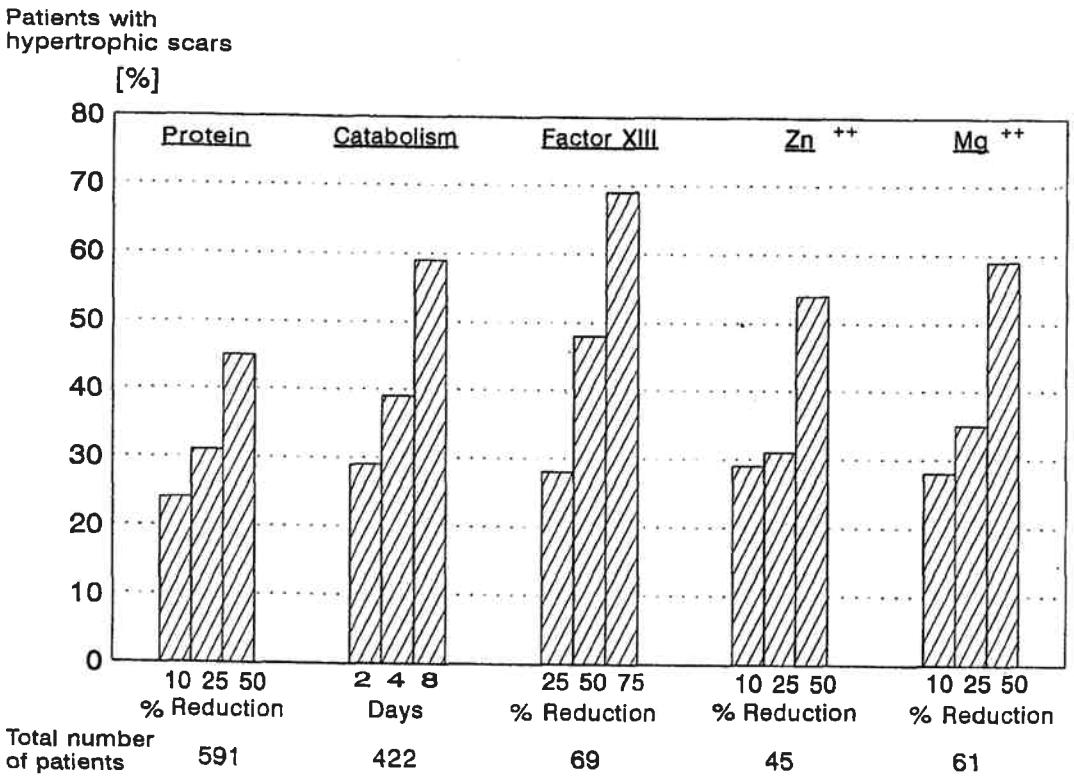

Fig. 1 Influence of metabolic factors on scar development.

tioned factors, a physiological or unphysiological scar can develop at the operation site.

On the basis of these findings and experiences and similar findings reported in the literature (1, 2) we made an assessment of scar development in children who underwent thoracic surgery and were subsequently treated with Contractubex gel containing the active ingredients onion extract, heparin and allantoin. The study was designed as an open trial in which a treated and an untreated group were compared.

Table Ia *Influence of general factors on scar development*

		Total no. of patients	Patients with hypertrophic scars [%]
Age	<1 year	2500	4
	>1 year		25
Dependence on localization		2500	yes
Infection preoperative		581	45
	postoperative	79	75
Wound oedema		771	55
Suture in traumatic area		641	59
Preterm removal of stitches		250	49

Table Ib *Influence of surgical factors on scar development*

	Total no. of patients	Patients with hypertrophic scars [%]
Wound tension	1250	30
Suture technique		
intracutaneous	2155	18
subcutaneous	2010	19
Steristrips	2045	15
Ischaemia at wound margins (i.op.)	410	80
Incisions at tension lines	2130	9

Patients and methods

Patients

A total of 99 young male and female patients who had undergone thoracic surgery (performed because of chest wall deformities, lung surgery or mediastinal tumours) were included in a clinical trial. The male patients underwent sagittal section, the female patients had a submammary section. Inclusion in the trial was only possible if the patients had no accompanying disease or had not received any comedication or other therapies which could have influenced scar development. Informed consent to participation had been obtained from all patients, from their parents or guardians.

Study design

This study was a prospective randomized, controlled study conducted in patients from the Clinic and Polyclinic for the Surgery of Children and the Newborn, Münster, Germany. One group received additional local treatment with Contractubex gel (components: 10% aqueous onion extract, 50 U heparin per g of gel, 1% allantoin) whereas the other group received only normal wound treatment. Treatment with Contractubex was usually begun after the discharge of the patients between days 14 and 21 after surgery. The patients or their parents were instructed to apply 2–3 cm of the gel to the scar tissue twice daily and to massage it lightly into the tissue. The total duration of treatment was six months.

The first examination was made before onset of treatment, followed by additional control examinations at regular intervals (usually monthly) over a period of six months. Another follow-up examination was made 12 months after commencement of treatment within the framework of clinical surveillance (after a six-month treatment-free interval). At the first examination, the case history was taken and the scar was characterized as to appearance (size, colour, scar type) and sensations at the scar site (itching). At the following examinations the scar

was evaluated with regard to size increase, colour, itching and scar type (appearance and consistency: physiological scar or hypertrophic or keloidal scar of varying degree of severity). Six months after the beginning of treatment or observation, the therapeutic result was assessed globally for all patients. In addition, in the Contractubex-treated patients, the tolerability of the product was evaluated and the occurrence of adverse events (AE) noted.

The efficacy of scar treatment was evaluated by comparison with untreated scars on the basis of the following parameters:
global evaluation of therapeutic result (4-point scale)
increase in scar size (4-point scale)
definition of scar appearance/consistency (6-point scale)
evaluation of scar colour (4-point scale)
assessment of itching (yes/no)
global evaluation of tolerability (4-point scale).

Statistical analysis

The statistical evaluations were made by means of SPSS/PC + V 4.01 or SAS version 6. The hypotheses of the superiority of Contractubex treatment as compared to non-treatment were tested on the basis of the above efficacy parameters using Fisher's exact test in the case of categorical data or ordered categorical data on the general error level of $\alpha = 0.05$. The group comparisons were made on the basis of the intent-to-treat sample (in the case of missing data using the "last value carried forward" criterion) at the end of the six-month treatment period or on the basis of the follow-up data after an additional six months.

In order to describe the course of the efficacy evaluation on the basis of individual characteristics, the median and the 1st and 3rd quartiles were calculated for each point of measurement according to Lienert's interpolation rule (1962) (3).

Results

Patient population

From the 99 patients originally included in the trial, 65 patients were evaluated. Only those patients were evaluated who were not older than 18 years, who exhibited physiological scar formation at the beginning of treatment or observation and who were examined at least once after 1–3 months and at least once after 4–6 months. A total of 34 patients not fullfilling these criteria were excluded from the evaluation, comprising 25 patients of the treated group and 9 of the untreated group, with no exclusion because of adverse events.

Thirty-eight of the Contractubex-treated patients (8 female/30 male) and 27 patients of the untreated group (9 female/18 male) were included in the global evaluation of the therapeutic result after the six-month observation period. Both groups were comparable as to age: in the Contractubex-treated group the mean age was 12.4 (3–18) yr and 11.3 (1–18) yr in the untreated group. In both groups, there were neither diseases nor application of any other medication or therapies which could have influenced scar development.

At the beginning of treatment, the size of the scars was comparable in both groups. In the treated group, the average length, width and height of the scars was 17.4 cm, 2.3 cm and 1.3 cm, respectively, as compared to 17.4 cm, 2.2 cm and 1.3 cm in the untreated group. The colour of the scars was also comparable in both groups. In the Contractubex group, 65.8% of the scars were reddened as compared to 70.4% in the untreated group. Itching was observed rarely, i.e., in one of 38 cases in the treated group and in two of 27 of the untreated cases. On average, the investigation of the Contractubex-treated patients started 29.8 days post-operatively and was carried out until the last examination after six months; in the untreated patients, the observation was, on average, begun 28.2 days after the operation.

Patients who underwent another six-month follow-up were evaluated separately. This evaluation was made for 21 Contractubex-treated patients and 14 untreated patients.

Efficacy

Comparing the treated group with the untreated group, the global evaluation of the therapeutic results showed a superiority of the Contractubex group over the untreated group after four to six months of treatment or observation. Whereas 84.2% of the treated patients showed a very good or good therapeutic result, a comparable result was achieved in only 59.1% of the untreated patients (Fig. 2). Tolerability was rated as "very good" in 37 of 38 cases and "good" in one patient. Adverse drug reactions were not observed.

The course evaluations of the parameters – increase in scar size, scar type, scar colour – described in the following are based on the data of the medium scar segment (medial) of both female and male patients. As itching occurred only in rare cases, it is not reported. The increase in scar size was classified as follows:

0 = hardly noticeable increase (<10%)
1 = slight increase (10–25%)
2 = marked increase (25–50%)
3 = pronounced increase (50–75%)

Figure 3 shows a comparable, hardly noticeable increase in scar size throughout the first two observation months for both treatment groups. From the 3rd to 4th observation month, there is a clear difference between the two groups in the course of the medians concerning the increase of scar size. Under treatment, there is a lower increase in scar size than without treatment. This difference continues to persist after the end of treatment ($p < 0.001$ after 6 and 12 months according to Fisher's exact test).

The appearance of the scar and its consistency were characterized according to the following scale:

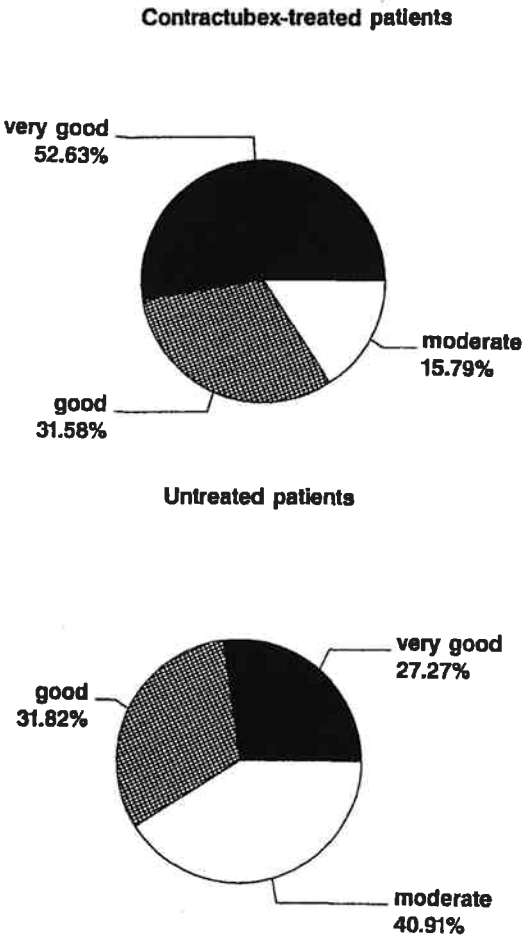

Fig. 2 Evaluation of the therapeutic result. (Patients with end points after 4–6 months).

1 = physiological scar
2 = homogeneous hypertrophic scar
3 = fine-nodular hypertrophic scar
4 = coarse-nodular hypertrophic scar
5 = weakly pronounced keloid
6 = strongly pronounced keloid

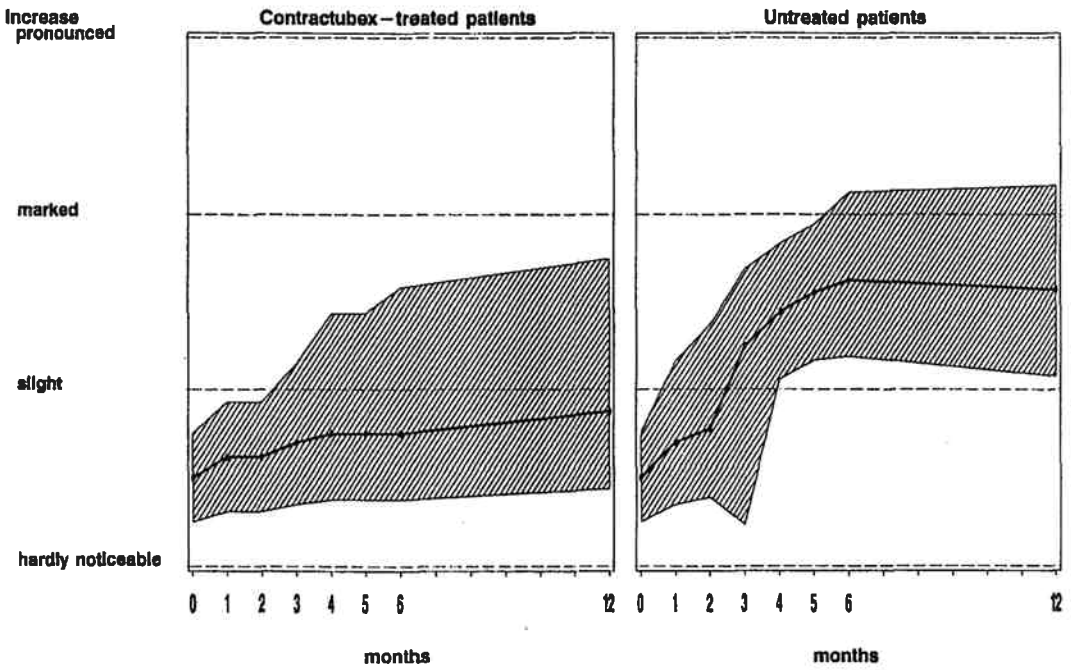

Fig. 3 Increase in scar size; patients with follow-up. Course of median and quartile range.

In the graph showing the course of the medians concerning the different scar types (Fig. 4) it can be seen that under Contractubex medication the conversion of primary physiological scars to unphysiological scars (hypertrophic or keloidal scars) is less frequent than without treatment. This difference in scar development continues to persist after the end of treatment ($p < 0.001$ after 6 months and $p < 0.05$ after 12 months in Fisher's exact test).

The colour of the scar was rated as depigmented/white, skin-coloured, faintly reddened or intensely reddened. In the course of the observation, a decrease in the number of patients showing (faintly or intensely) reddened scars was seen in both groups: in the treated group from 52% to 14% (after 6 months) and 0% (after 12 months) and in the untreated group from 64% to 57% (after 6 months) and 21% (after 12 months). However, probably because of the small sample size ($n = 14-21$), the significance level was not reached either after 6 or after 12 months.

Discussion

The development of a scar is based on a sequence of finely attuned wound healing processes. In the ideal case, the wound heals by leaving a relatively fine "line", which, in comparison with the surrounding skin, is slightly lighter in color. Unphysiological wound healing, on the other hand, can result in the formation of an enlarged, elevated,

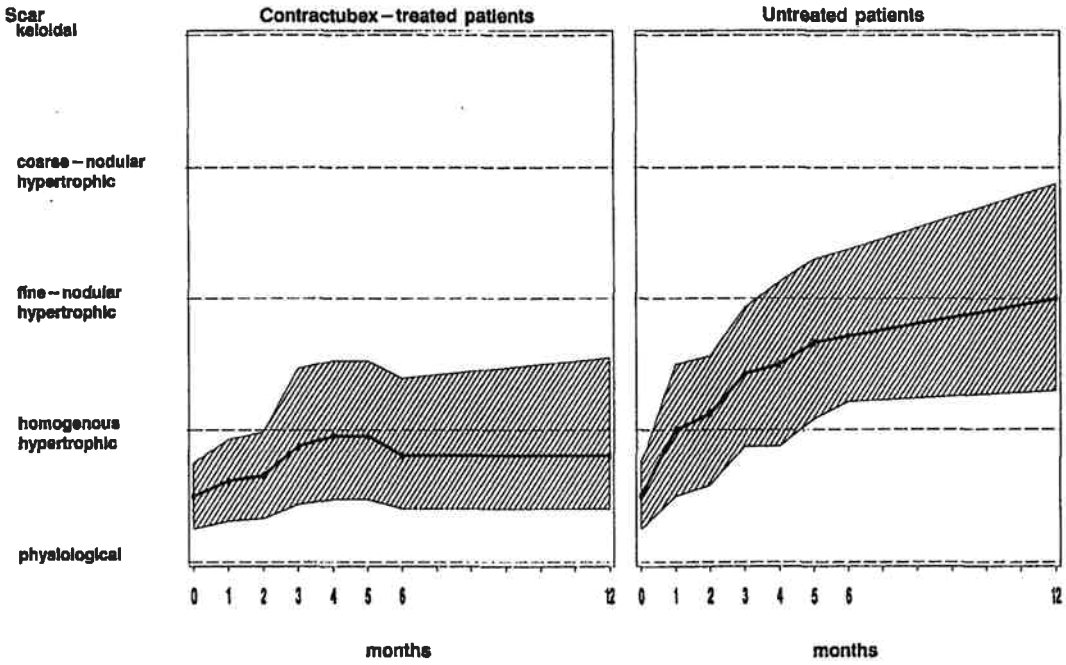

Fig. 4 Definition of scar appearance; patients with follow-up. Course of median and quartile range.

reddened and even itching scar "cord".

The most important causes of unphysiological scar development after thoracic surgery are thought to be the age of the patient and the localization of the scar. Very frequently, there is a tendency in young patients before and at puberty to form hypertrophic and keloidal scars. As the chest is regarded as an unfavourable site for physiological scar formation (1, 4), the risk of developing hypertrophic or keloidal scars has to be minimized. As fully developed keloids are difficult to treat, preventive treatment is preferable to curative scar treatment (1).

In this study, fresh scars in the thoracic region were treated with Contractubex which has been used in scar therapy for more than 20 years. The therapeutic results obtained with Contractubex after the preventive treatment of surgical scars, which have been presented in other publications (5, 6), could be confirmed. Accordingly, in the present study, a six-month treatment of fresh surgical scars led to a decreased formation of unphysiological scar types and to a cosmetically satisfactory result.

The comparison of treated and untreated scars reveals that in the treated group the increase in scar size was smaller than in the untreated group. In addition, the treated scars showed a tendency towards quicker paling. All assessments after the six-month treatment-free follow-up demonstrate that the effects of therapy continued to persist after the end of treatment. In the treated group, both scar type and appearance are rated much more favour-

ably than in the untreated group, even after the treatment-free follow-up.

The observed scar-specific effects can be explained by the pharmacological effects of the individual ingredients in Contractubex or of their combination. In an early phase of scar formation, which is characterized by inflammatory signs, it is especially heparin and onion extract (or its compounds) that influence scar development by their inhibitory effects on inflammatory processes (7–9) and fibroblast proliferation (10) as well as on the synthesizing capacity of fibroblasts (e.g. collagen synthesis) (11). In a later phase, which is further characterized by connective tissue fibres, a loosening effect on collagen structure is achieved by the combination of onion extract, heparin and allantoin (12). The polyelectrolytes heparin and allantoin have a hydrating effect (13–16) which, in addition, promotes the softening of the indurated scar structures.

In summary, it could be shown that early treatment with Contractubex is suitable for reducing the risk of developing pathological scars after thoracic surgery. In addition, the scar-specific is well tolerated and permanently improves the appearance of scars.

References

(1) Loosli R.M., Krupp S. *Die pathologische Narbe. Interessante Erkenntnisse über Prophylaxe und Korrektur*, Dia, **11**, 17–23, 1982.

(2) Murray J.C., Pollak S.V., Pinnel S.R. *Keloids: A review*. J. Am. Acad. Dermatol., **4**, 461–470, 1981.

(3) Lienert G.A. *Verteilungsfreie Methoden in der Biostatistik*, 3., um einen Nachtrag erweiterte Auflage., A. Hain, Meisenheim am Glan, Band I, 1962.

(4) Krupp S. *Zur Nachbehandlung von Hautnarben*. Therapeutische Umsch, **37**, 787–790, 1980.

(5) Stein G. *Das Keloid. Gedankengänge zur Therapie*. Fortschr. Med., **93**, 1107–1112, 1975.

(6) Stein G. *Erfahrungen mit der Behandlung von Keloiden und hypertrophen Narben unterschiedlicher Genese mit Contractubex comp*. Therapiewoche, **35**, 1199–1209, 1985.

(7) Carr J. *The antiinflammatory action of heparin: Heparin as an antagonist to histamine, bradykinin and prostaglandin E_1*. Thrombosis Res., **16**, 507–516, 1979.

(8) Dorsch W., Ring J. *Suppression of immediate and late anti-IgE-induced skin reactions by topically applied alcohol/onion extract*. Allergy, **39**, 43–49, 1984.

(9) Rudolph C., Tauschel H.D. *Untersuchungen zur perkutanen Wirksamkeit einer Heparin-Allantoin-Dexpanthenol-Kombination in spezieller Salbengrundlage: Antiallergische/antiinflammatorische Wirkung im PCA-Test bei der Ratte*. Arzneimittelforsch., **34**, 1766–1768, 1984.

(10) Majewski S., Chadzynska M. *Effects of heparin, allantoin and cepae extract on the proliferation of keloid fibroblasts and other cells* in vitro. Dermatol. Monatsschr., **174**, 106–129, 1988.

(11) Janicki S., Sznitowska M. *Effect of ointments for treating scars and keloids on metabolism of collagen in scar and healthy skin*. Eur. J. Pharm. Biopharm., **37**, 188–191, 1991.

(12) Heine H. *Narbenbehandlung durch transepidermale Heparinisierung-Wirkungsweise eines Narbenspezifikums*. Therapeutikon, **3**, 369–375, 1989.

(13) Beiglböck W., Sickel K., Clotten R. *Heparin als Heilmittel für mesenchymale Gewebe*. Münch. med. Wschr., **9**, 410–416, 1952.

(14) Goy H. *Allantoin und seine Derivate*. Seifen-Öle-Fette-Wachse., **100**, 349–352, 1974.

(15) Jaques L.B. *Heparin: A unique misunderstood drug*. Trends Pharmacol. Sci., **3**, 289–291, 1982.

(16) Mecca S.B. *The function and applicability of the allantoins*. The Toilet Goods Association, **39**, 7–15, 1963.