Treatment of ichthyosis—There is always something you can do! In Memoriam: Wolfgang Küster

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We have lost a good friend, dermatology has lost a cherished colleague at a far too early age, and patients with ichthyosis and other disorders of keratinization have lost one of their staunchest supporters, Wolfgang Küster (Fig 1).

Wolfgang was born in Kassel, Germany, on June 17, 1953, and spent the first two decades of his life there. He studied medicine in Münster, Germany, and in Vienna, graduating in 1980. Stimulated by the famous human geneticist in Münster, Widukind Lenz, who had identified the thalidomide embryopathy, Wolfgang first studied human genetics in Münster and then Düsseldorf, where he became board certified. Not satisfied to diagnose genetic disorders, Wolfgang also wanted to help these often-neglected patients and thought dermatology would be the best route to this goal. He trained in Düsseldorf with Gerd Plewig, did his habilitation on lipids in disorders of keratinization, and then joined Rudi Happle in Marburg where he was on the faculty for 6 years. The last 9 years of his life, Wolfgang was director of the TOMESA Specialty Clinic for Dermatology in Bad Salzschlirf, a large private clinic where he was able to develop an extensive practice in caring for disorders of keratinization and other genetic disorders and severe skin diseases such as psoriasis and atopic dermatitis.

Fig 1. Wolfgang Küster, 1953-2006.

Wolfgang's dedication to his patients influenced everyone who had contact with him. He had almost limitless energy when it came to studying and caring for patients with ichthyosis. Part of this engagement came from his family; Wolfgang's second wife, Sabine Wiegandt, was for many years chairperson of Selbsthilfe Ichthyosis e.V. (Self-help Group for Ichthyosis) in Germany. Two of her three children have lamellar ichthyosis with transglutaminase deficiency; thus, Wolfgang had two stepchildren with whom he enjoyed working daily to perfect his therapeutic approach to this genodermatosis. In addition, he worked tirelessly with the self-help group and other professional organizations to correct a travesty of false economy in dermatologic therapy. Wise administrators decided that urea-based compounds were skin care products, not medications, and thus need not be paid for by health insurance companies. Through much political activity, this decision was reversed so that at least patients

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with ichthyosis could receive urea products on a prescription basis.

Wolfgang had considerable intellectual curiosity. His training in two disciplines had convinced him of the need for cooperative or interdisciplinary research. He was one of the driving forces behind the establishment of the Network for Ichthyoses and Related Keratinization Disorders (NIRK), a federally sponsored program established in 2003 as part of a drive to devote more resources to rare diseases.[1] The network attempts to link basic science researchers, clinical researchers, practicing physicians, and patient groups into an effective team to address the many outstanding questions in this area. NIRK today is addressing projects dealing with CHILD syndrome, palmoplantar keratoderma (PPK), lamellar ichthyosis, and gene therapy for Sjögren-Larsson syndrome.

Wolfgang left behind a written legacy of around 100 scientific articles, almost all dealing with some aspect of genodermatoses. One of his most important articles clarified the cloudy situation surrounding Unna-Thost and Vörner PPK. It had long been believed that Vörner PPK with the distinctive histologic finding of epidermolytic hyperkeratosis was a relatively rare disorder, whereas the most common form of PPK was Unna-Thost variant in which there was only marked hyperkeratosis and acanthosis. No physician or patient enjoys a palmar or plantar biopsy, so it was easiest to follow this conventional wisdom, but fortunately Wolfgang was curious and produced some surprising results. He identified members of the original family studied by Thost and biopsied them, finding epidermolytic hyperkeratosis and confirming that Thost and Vörner PPK are identical.[2] Later he and others identified very similar mutations in keratin 9 for patients from both Thost's and Vörner's original families.[3]

His last article, published in November 2006, dealt with a peculiar medical mystery that he and NIRK helped solve. Bathing trunk ichthyosis is a peculiar form of lamellar ichthyosis in which the patient is born as a collodion baby, and then has widespread ichthyosis that persists on the trunk but resolves on the extremities. Members of NIRK combined forces to show that the explanation is a temperature-sensitive mutation in transglutaminase-1, the enzyme responsible for the most common type of lamellar ichthyosis. The enzyme is effective enough in cooler body regions, but in warmer areas it cannot meet the metabolic demands and keratinization is abnormal.[4]

In our estimation, Wolfgang's greatest contribution to dermatology was his insistence that every patient with ichthyosis or PPK could be helped by highly individualized therapy. He was actively opposed to the usual dermatologic approach of explaining to the patient that they have a rare genetic disease for which there is no cure and only limited therapeutic options. Instead, he worked tirelessly with each of his patients to try to find a treatment plan that worked. One of his last articles appeared in the

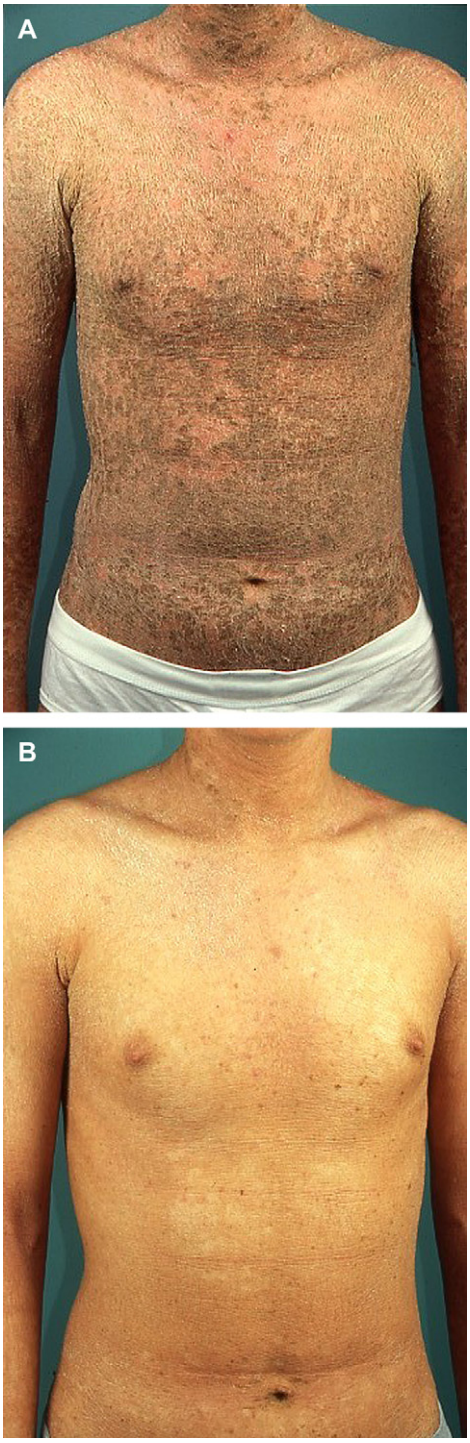

Fig 2. Patient with lamellar ichthyosis before therapy (**A**) and after using only topical methods discussed in this article (**B**). Reproduced with permission of *Deutsches Ärzteblatt*.[5]

Table I. Guidelines for individualized therapy

Congenital ichthyosis (neonatal intensive care)
Monitor fluid balance, electrolytes; watch for skin infections
Incubator with high humidity but somewhat lower temperature; remember infants may have trouble with sweating; monitor temperature
Never bathe without relubricating; apply nonmedicated cream thinly 6-8 times a day
Ectropion management by ophthalmology
Watch for flexural contractures
Check vision and hearing; get neurologic evaluation
Put family in touch with ichthyosis self-help group
Newborns and infants
Bathe twice daily with sodium bicarbonate
Rub lightly with soft washcloth or microfiber towel
Apply nonmedicated cream 2-3 times daily
No urea or salicylic acid
Ectropion management by ophthalmology; cleaning of external ear by otorhinolaryngology
Physical therapy to avoid flexural contractures
Children
Bathe twice daily with sodium bicarbonate
Rub with soft washcloth, microfiber towel, or pumice stone
Apply 5% urea cream twice daily
Treat scalp with stronger urea cream 7%-10%
Ectropion management by ophthalmology; cleaning of external ear by otorhinolaryngology
On warm summer days, measure temperature, force fluids, cool environment, no occlusive ointments; play outside earlier or later, not in midday
No vacations in warm climates

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Deutsches Ärzteblatt (a journal distributed to every German physician) in June of 2006, and was entitled "Ichthyosen: Vorschläge für eine verbesserte Therapie".[5] One of us (W. H. C. B.) contacted Wolfgang to help translate this article into English, but never received an answer. With the help and permission of Dr Christopher Baethge, Medical-Scientific Editor of the *Deutsches Ärzteblatt*, we now present paraphrased excerpts of Wolfgang's last article translated into English to make this important clinical concept available to more readers. The material taken from the German article is printed in italics.

ICHTHYOSES: SUGGESTIONS FOR IMPROVED THERAPY

Introduction

A MEDLINE search for "ichthyosis therapy" from 1990 to 2005 revealed 262 citations but only 4 controlled studies. Only a few clinical centers concentrate on ichthyoses, which are both rare and heterogenous. Following up patients for years gives one insight into the effectiveness and safety of a given therapy. In the past 20 years in the university dermatology departments in Düsseldorf and Marburg and the TOMESA Clinic in Bad Salzschlirf, I have treated 692 patients with ichthyosis and had the opportunity to observe them, their problems, and their response to therapy. Despite the marked differences in both gene defect and clinical manifestations of the many forms of ichthyosis,[6] the same general approach to therapy can help almost all these patients. I have tried many approaches not previously reported that have enabled me to develop a beneficial treatment plan for almost all my patients. Table I summarizes my approach.

Newborns

Newborns with congenital ichthyosis are often premature. Many present as a collodion baby surrounded by a thin membrane that splits soon after birth and is lost in the first weeks of life. Left behind is erythematous skin that, during a period of weeks, begins to develop scales of varying intensity. These patients require intensive nursing care, as their skin is not capable of normal water retention or temperature control. Setting the incubator temperature requires a fine touch. If it is set too high, they may become erythematous and have a fever that is mistaken for an infection; if too low, they get cold. Their abnormal skin barrier can also lead to electrolyte imbalance and infections. If there are no nondermatologic contraindications, they should be bathed 1 to 2 times daily and lubricated with a thin, nonocclusive cream 6 to 8 times daily to restore the

Table II. Keratolytic or hydrating substances with usual maximum concentration

Agent	Maximum concentration (%)
Urea	10
NaCl	10
Lactic acid*	5*
Salicylic acid only for stubborn areas	10
Tretinoin	0.05
Glycerin	10
Vitamin E acetate	5
Dexpanthenol	5
Propylene glycol	15

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*Lactic acid much better in optimized buffered commercial preparations where 12%-14% concentrations can be achieved that are well tolerated.

Table III. Two favorite prescriptions

5% urea cream for body (water in oil)	
Urea	5.0 g
Lactic acid	1.0 g
Sodium lactate 50%	4.0 g
Water	35.0 g
Glycerin	5.0 g
Aquaphor Original*	ad 100.0 g
Shelf life: 6 mo	
Urea scalp cream	
Urea	7.0-10.0 g
Lactic acid	1.0 g
Sodium lactate 50%	4.0 g
Propylene glycol	10.0 g
Water	40.0 g
Basic cream DAC	ad 100.0 g
Shelf life: 6 mo	

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DAC, Deutscher Arzneimittel-Codex.
*Manufactured by Beiersdorf, Norwalk, CT.

normal moisture and reduce scale formation to a minimum. Creams with salicylic acid cannot be used in this setting; absorption is dramatic and metabolic acidosis can occur rapidly and be life threatening.

Bathing

Regular bathing, even more than once daily, is important for many reasons. Both scales and residual medications are loosened, while at the same time, the skin is tanked up with the water is has lost because of the imperfect barrier. The loosened scales can then be removed mechanically. Neither oil nor salt bath additives are ideal; the former is messy and may be occlusive, whereas the latter can be irritating. Instead, I have found sodium bicarbonate ($NaHCO_3$), commonly known as baking soda, most effective.

Several handfuls in a tub of water are required. By denaturing the keratin and making the water alkaline, it helps remove scales. Of the more than 350 inpatients I treated with $NaHCO_3$ baths, more than 70% profited from this approach. Other agents that can be tried if $NaHCO_3$ is not helpful include wheat starch, corn starch, and rice starch.

A steam bath is even better for softening scales but is not widely available. Patients with bullous ichthyoses such as congenital ichthyosiform erythroderma Brocq tend to have foul-smelling areas of maceration, which is a major social problem. Antiseptics such as 0.1% octenidine or 0.1% polihexanide can be added to bath water or applied afterward.

Mechanical scale removal

Mechanical removal of scales after bathing is more efficient than the use of keratolytics. After trying many different ways of rubbing away scale, I have found that microfiber household towels, pumice stones, and special silk from China are most effective. Effective, relatively painless scale removal by repetitive gentle rubbing can be achieved in the bathtub once the patient has soaked for 30 minutes. The process is easier to describe than to do—it requires training, is physically exhausting, and lasts at least 1 hour if the entire body is affected. The required interval is between twice daily and twice weekly. A bland cream must be applied immediately after getting out of the tub.

Topical therapy

Newborns and small children should be treated with a medication-free vehicle base. The ratio of body surface area to weight is 2.5-fold larger than in adults, so that the resorption of topical substances is proportionately higher. In addition, the skin is more sensitive so that most keratolytics are not tolerated. Later a number of compounds can be considered for use (Table II). Topical corticosteroids are not in this group; their use is contraindicated for treating ichthyosis.

Urea is the most important active ingredient in ichthyosis therapy. It is a classic humectant, binding water and facilitating epidermal barrier regeneration, with additional keratolytic and antimicrobial effects. It should not be used in the first year of life because of irritation and risk of elevated blood levels.

Salicylic acid is an effective keratolytic but is too well absorbed. It is contraindicated in infants and

small children and is best used in older children and adults to treat limited stubborn areas.

Tretinoin (0.025%-0.05%) is also keratolytic but irritating, especially because after a few applications it causes fine barely visible but painful fissures. In addition, with widespread use, there is enough absorption to raise the issue of teratogenicity and make its use in females of childbearing age inadvisable.

Additional agents are considered in the Table II. Lard (Adeps suillus) can be used to loosen thick crusts on the scalp, palms, and soles. Glycerin is helpful to improve skin flexibility for those patients with stiff or armorlike scales.

Because of the tremendous individual variation in skin sensitivity and response, the therapy must be optimized for each patient. The best way of doing this is to do side-by-side comparisons, treating each half of the body differently. To increase the effectiveness of keratolytics, troublesome areas can be wrapped with clear household wraps for a few hours or overnight. Because of problems with temperature control, large areas should never be so occluded.

The scalp requires special attention. Many patients have thick plates on the scalp that are often secondarily infected, malodorous, and lead to scarring alopecia. The trick is prolonged occlusion, using a washable urea cream at night under occlusion. Finally the scalp can be soaked in the tub by older children, who enjoy diving or the contortions required. After gentle washing, the scales and crusts are teased off.

Most patients with ichthyosis require 4 different topical agents: a washable cream for the scalp, a low-concentration cream for the face, a midconcentration cream for routine use on the body, and a special high-strength preparation for intermittent use in problem areas. The reality is that most patients must bathe twice daily and frequently rub their skin for debridement. A teenager or adult will require 2 to 3 kg monthly of their basis midconcentration cream or ointment. Patients with ichthyosis require so much topical medication that considerable cost savings can be achieved by compounding (Table III).

Quite remarkable improvement can be achieved by following this regimen (Fig 2). Wolfgang went on to discuss in similar detail the following fine points of ichthyosis therapy that we have summarized in telegraphic style:

Ocular problems: Ectropion can often be avoided by regular lubrication and use of artificial tears. Surgical correction is possible.

External ear: Accumulation of debris often leads to impaired hearing, a totally unnecessary disability for these children. The eardrum may also be affected by the disease.

Contractures: Regular physical therapy and later activity is essential to avoid contractures secondary to stiffened skin.

Systemic retinoids: Some forms of ichthyosis benefit dramatically from systemic retinoids. For example, harlequin ichthyosis is no longer universally fatal because of the early use of acitretin. The acute problem is always irritation, especially for patients with erythematous forms of ichthyosis, whereas chronic problems include teratogenicity, lipid abnormalities, and irreversible skeletal changes.

Anhidrosis: Problems with sweating are often overlooked for patients with ichthyosis. When the outside temperature is above 70°F, patients should be careful, avoiding strenuous activity and increasing fluid intake. Both heat stroke and febrile convulsions are very real risks.

Inpatient training: Wolfgang and his coworkers devoted considerable energy to teaching patients with ichthyosis and their parents how to care for the disease.

Genetic counseling should be offered to all affected families.

Psychosocial issues: Ichthyosis is a stigma for every patient, as almost invariably the visible skin surfaces are affected, leading to social rejection. Therapy is difficult, expensive, and time-consuming, and produces improvement, not cure. These patients deserve social support, as offered by NIRK, and in many instances require professional psychologic care. In Germany, patients, even small children, are estimated at 70% to 100% disabled and then eligible for financial help for medications and nursing support.

The article was much longer than this perhaps too brief summary, completely demonstrating Wolfgang's devotion to patients with ichthyosis, considering care at every age group, emphasizing a multidisciplinary approach, and expressing concern for social and financial issues. It is his legacy to a group of patients who meant so much to him.

Wolfgang Küster died suddenly, probably from a cardiac arrest. His wife, Sabine, told one of us (H. T.) that he had been restless in the weeks before his death, full of plans for new projects but still uncertain about the future. One can almost imagine that he had somehow anticipated that he was running out of time. H. T. had dinner with Wolfgang 2 weeks before his death, at a meeting in Freiburg, and found him in good spirits and pleased with the progress of dermatologic genetics. He was looking forward to participating in Germany's oldest and most-famous

continuing medical education program for dermatologists, the 20th Fortbildungswoche für praktische Dermatologie und Venerologie in Munich on July 23 to 28, 2006. The title of his last talk—one that he never gave—was "Therapie der Ichthoysen: Es geht immer was." In English, this would have been "Treatment of ichthyosis—there is always something you can do!" This is a fitting legacy for Wolfgang Küster, our friend and colleague, who died on July 24, 2006, just a few days before his talk. We will always remember him for his tireless devotion to patients with ichthyosis and disorders of keratinization.

Sabine Wiegandt, Wolfgang's widow, enthusiastically supported this work. Dr Christopher Baethge, Medical-Scientific Editor of the *Deutsches Ärzteblatt* allowed us to translate Wolfgang's article and reproduce the before-and-after photographs. Dr Marie-Luise Preil, Wolfgang's associate in Bad Salzschlirf, miraculously found the original photographs and provided them to us. Dr Gerd Wolf, an expert in pharmaceutical compounding, helped us "Americanize" Wolfgang's favorite compounded prescriptions.

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