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# Uremic Pruritus

## Clinical and experimental studies

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Stockholm 1989

This thesis is based on the following papers, which will be referred to by their Roman numerals.

I. Ståhle-Bäckdahl M, Hägermark Ö, Lins L-E. Pruritus in patients on maintenance hemodialysis. Acta Med Scand 1988;224:55-60.

II. Ståhle-Bäckdahl M, Wahlgren C-F, Hägermark Ö. Computerized recording of itch in patients on maintenance hemodialysis. Acta Derm Venereol (in press).

III. Ståhle-Bäckdahl M, Hägermark Ö, Lins L-E, Törring O, Hilliges M, Johansson O. Experimental and immunohistochemical studies on the possible role of parathyroid hormone in uremic pruritus. J Intern Med (in press).

IV. Ståhle-Bäckdahl M. Stratum corneum hydration in patients undergoing maintenance hemodialysis. Acta Derm Venereol 1988;68:531-534.

V. Ståhle-Bäckdahl M, Hägermark Ö, Lins L-E. The sensitivity of uremic and normal human skin to histamine. Acta Derm Venereol 1988;68:230-235.

VI. Johansson O, Hilliges M, Ståhle-Bäckdahl M. Intraepidermal NSE immunoreactive nerve fibres - evidence for sprouting in uremic patients on maintenance hemodialysis. Neuroscience Lett (in press).



ISBN 91-7900-712-0

# Abbreviations

PTH parathyroid hormone

UVA long-wave ultraviolet light

UVB middle-wave ultraviolet light

AU arbitrary units

AUC area under the curve

VAS visual analogue scale

NSE neuron-specific enolase

## CONTENTS

# Introduction

The introduction of maintenance hemodialysis in the 1960's meant survival for patients previously doomed. In Europe today more than 75 000 people are being treated with chronic hemodialysis and an additional 10 000 with peritoneal dialysis (1). The knowledge and understanding of renal physiology is rapidly increasing and the kidney is being recognized not merely as an organ with excretory but with substantial metabolic and endocrine activity as well. Over the years the dialysis technique has steadily improved, patients' long-term survival has increased and they are free from gross uremic symptoms such as nausea and severe hypertension. Still, it is evident that dialysis treatment only partly compensates for the loss in renal function, and despite the therapeutic improvements various uremic symptoms such as pruritus remain a clinical problem.

## Pruritus - general aspects

Itch is a sensation that provokes the desire to scratch. It is commonly associated with dermatologic diseases but may arise without obvious skin affection in conjunction with systemic disorders such as obstructive biliary disease, lymphoma and chronic renal failure. Itch may constitute a major clinical complaint and often represents a diagnostic and therapeutic challenge. The subjective nature of itching makes its assessment extremely difficult and the evaluation of pruritus is therefore an intricate task for clinical investigators.

The neuroanatomical and neurophysiological bases for the pruritic sensation are insufficiently understood. It is generally accepted that itch is mediated in thin unmyelinated nerve fibers (2). No specific itch receptor has so far been disclosed morphologically but in experimental studies Arthur and Shelley demonstrated that maximal itch was elicited from a limited zone close to the dermo-epidermal junction (3). The afferent nerve fibers enter the spinal cord mainly via the dorsal root where sensory impulses are coordinated and integrated with those of other afferents. Itch impulses are transmitted centrally via the spinothalamic tract. The supraspinal structures activated in pruritic conditions are unknown, but itch may arise in association with cerebral processes such as tumours, abscesses and lesions of multiple sclerosis (4,5,6). The perception of itching is modified by psychological influences such as stress, anxiety and distraction (7,8,9), and central structures may control spinal transmission of cutaneous inputs via descendent pathways.

The sensation of itch can be elicited by various kinds of chemical, electrical and mechanical stimuli (10,11). Histamine is the best known endogenous pruritogenic substance and is thought to play a major role in the pathogenesis of urticaria. The pathophysiology of itching in other disorders is basically unknown. There is usually no sign of hi-

stamine release, i.e. wheal and flare reactions, and antihistaminic drugs give poor relief. Other substances, e.g. the neuropeptide substance P, which induce a "true" itching sensation when injected intracutaneously, seem to do so by releasing histamine, and their action can be blocked by antihistamines (12). Thus, in most pruritic clinical conditions the pathogenesis remains to be clarified.

## Uremic pruritus

Uremic pruritus is a manifestation of chronic and terminal renal failure. It is not associated with acute renal insufficiency (13). Itching can start before or after the initiation of dialysis treatment (14,15). Symptoms may subside with treatment, and remission of pruritus has been reported in 40% of maintenance dialysis patients (16), while in other patients pruritus persists through months or years of treatment.

In 1932 Chargin & Keil reported that 12-20% of patients with chronic renal insufficiency suffer from pruritus (13). In more recent surveys comprising patients on dialysis treatment the incidence of pruritus varies between 60-80% (14,15,17). The reason for the increased prevalence of pruritus is not known, but frequently hemodialysis in itself has been blamed for inducing and worsening the symptoms. In support of this, Gilchrest found an association between the bouts of itching and the hours of treatment (16). On the other hand, the observation that pruritus is often present before the initiation of dialysis and occurs in patients on hemodialysis as well as peritoneal dialysis (15,17) would suggest that pruritus is due to the metabolic disturbances of chronic renal failure and is bound to occur more frequently with prolongation of life by treatment.

Uremic itching can be localized, affecting only parts of the body, or generalized. It can appear in paroxysms or be more or less continuous. Symptoms can vary from mild itching hardly bothering the patient to severe symptoms preventing sleep. Thus, no consistent pattern of uremic pruritus has hitherto been disclosed.

## Uremic pruritus - pathophysiological considerations

The etiology of uremic pruritus is unknown. Various possible explanations have been put forward, but so far no definite causality has been proven.

Theoretically, itching might be elicited in different ways. Pruritogenic substances may accumulate due to deficient excretion or altered metabolism. These substances might exert their effect on peripheral "itch receptors" in the skin or upon "itch centers" in the brain. Another hypothesis is that metabolic disturbances might cause pathological changes in the skin e.g. affecting vascular tissue, nerve fibers, barrier function etc. which indirectly might induce a pruritic condition. Besides the metabolic derangements inflicted by the state of renal insufficiency, the dialysis treatment in itself is discussed in the pathogenesis

of various acute and chronic complications. During the early development of dialysis, the emphasis was on its separation and blood purification functions, but today the artificial kidney is viewed not merely as a separator but rather as a bioreactor in which a variety of complex biological reactions occur. Recently the "Interleukin hypothesis" has been proposed (18,19). The central idea is that mononuclear phagocytes in the blood of dialysis patients produce interleukin-1 in response to C5a activation following contact between plasma and the dialysis membrane and are also stimulated by endotoxin fragments in contaminated dialysate fluids (20). Interleukin-1 is not pruritogenic in itself (21) but it induces the release of inflammatory and potentially pruritogenic substances. However, the whole concept is purely speculative and its clinical significance awaits verification. Still, there is a continuous endeavor to develop dialysis membranes of greater biocompatibility. The pathophysiology of uremic pruritus has been attributed to a host of different factors. The main interest has been focused on some theories which will be briefly presented.

Secondary hyperparathyroidism with high serum levels of parathyroid hormone (PTH) has been implicated in the pathogenesis of various uremic complications, including pruritus. Prompt disappearance of itching is described following parathyroidectomy in dialysis patients (22,23). Pruritus may recur postoperatively if the patients are made hypercalcemic despite low levels of PTH (23). However, there is no clear-cut pattern since not all patients with secondary hyperparathyroidism suffer from itching, nor is pruritus a manifestation of primary hyperparathyroidism or other hypercalcemic conditions.

Derangements of other divalent ions, phosphate and magnesium, have also been proposed as etiologic agents. Uremic skin has a high content of calcium, magnesium and phosphate. Blachely et al demonstrated a significant reduction of skin phosphorous content after ultraviolet irradiation (UVB) in dialysis patients suffering from pruritus (24). A positive correlation between serum magnesium levels and pruritus was recently reported (25) and in one case relief of pruritus followed lowering of dialysate magnesium concentration (26). However, in a controlled study comprising 17 patients treated with magnesium free dialysate, there was no reduction of itching despite lowered serum magnesium concentrations (27).

Uremic skin undergoes considerable gross changes; it becomes atrophic, xerotic and assumes a yellowish discoloration (28,29). The xerotic skin texture is often referred to as "dry skin" and has been suggested as a cause of uremic pruritus. Young reported a positive correlation between the degree of xerosis and severity of pruritus (14). However, the pathogenetic mechanisms responsible for the skin roughness are not fully understood and its possible significance for the development of itching remains to be established.

Increased serum levels of vitamin A accompany chronic renal failure possibly as a result of a decrease in renal clearance of retinol-binding protein (RBP) (30,31). Xerotic and

itchy skin of hypervitaminosis A resembles the skin lesions of uremia. Berne et al reported decrease of epidermal retinol in ten dialysis patients and a concomitant relief of pruritus in seven of the ten patients following exposure to ultraviolet light, suggesting a role for vitamin A in the etiology of uremic itching (32). However, other studies have failed to show any correlation between serum levels of vitamin A and the severity of pruritus (33).

Histamine elicits itching upon intracutaneous injection and has been proposed as a mediator in most itching conditions including that occurring in chronic renal failure. Elevated plasma histamine levels have been reported in dialysis patients (34). However, intravenous infusion of histamine does not cause itch (35) and whether high concentrations of circulating histamine induce itching is an open question.

It has been reported that parathyroid hormone administered experimentally stimulates mast cell accumulation in bone and spleen in rats (36) and it has been suggested that high levels of PTH might induce mast cell proliferation in uremic patients (37). Mastumoto described a significant increase of dermal mast cells in patients undergoing hemodialysis treatment (38). However, in a recent study there was no difference in the number of cutaneous mast cells between pruritic and non-pruritic dialysis patients (39).

Polyneuropathy develops in a majority of patients with chronic renal failure (40). Uremic neuropathy affects motor, sensory and autonomic nerve fibers, and although experimental evidence is lacking, it has been discussed whether pruritus is a manifestation of neuropathic disturbances in these patients (41).

## Therapeutic attempts

The evaluation of antipruritic therapy is a veritable challenge in clinical research. The variety of different treatments attempted for uremic pruritus, such as activated charcoal, cholestyramine, heparin, lidocain, antihistamines etc (42-47) suggests insufficient efficacy or intolerable side effects. As yet the only lasting cure appears to be a successful renal transplantation (48).

The most promising therapy during the last decade is ultraviolet irradiation within the sunburn spectrum (UVB). This seems to provide at least temporary relief for many patients (49,50). Long-wave ultraviolet light (UVA) might have a similar although less convincing effect (51). The possible mode of action is unknown, but photo-inactivation of pruritogenic substances, the formation of photo-products relieving itching or the activation of vitamin D altering divalent skin ions have been advanced as possibilities (52). However, one must concede a substantial placebo effect from any antipruritic therapy. Taylor et al found that treatment with both UVA and placebo significantly suppressed uremic itching in eleven dialysis patients (53).

# Aims of the study

The aims of the present study were to study clinical aspects of pruritus in patients on maintenance hemodialysis and to evaluate some putative pathogenic factors in the skin namely:

parathyroid hormone, its possible role as a peripheral mediator of uremic itching,

xerosis, the relation between the clinical appearance of "dry skin", stratum corneum hydration and pruritus,

sensitivity of uremic skin to experimental itch induced by histamine.

neuronal structures in uremic skin evaluated by histochemical technique.

# Subjects, Material and Methods

## Subjects (I-VI)

All patients participating in the study suffered from chronic renal failure and were being treated with maintenance hemodialysis at the Division of Nephrology, Department of Medicine, Karolinska Sjukhuset. Five patients treated at Södersjukhuset took part in study II. Healthy controls were recruited from hospital staff, friends and family. Subjects are presented in Table I. Underlying renal diseases in 77 patients (29 patients in study I + 48 patients examined 20 months later) are given in Table II.

## Characterization of itch (I,II)

Patients were questioned about the severity, localization and characteristic features of pruritus. Pruritus was classified as being: absent 0; mild + (nearly constant, not disturbing the patient); moderate ++ (nearly constant, disturbing the patient) or severe +++ (constant pruritus, disturbing sleep). The intensity of itching was assessed in 28 patients (II) using visual analogue scales (VAS) and the Pain-Track, which is a portable data logger and a software package for storage and analysis of data (54). Measurements were performed during seven days including three dialysis sessions (Fig 1).

## "Dry skin" (I, IV)

In paper I, 29 dialysis patients underwent dermatologic examination. The clinical appearance of the skin and the presence of xerosis were noted. In paper IV we attempted a more detailed evaluation of the "dry skin" in 31 dialysis patients, 19 with and 12 without pruritus. Twelve healthy subjects matched for age and sex served as controls. The degree of xerosis was estimated in three different body sites, the neck, the chest and the lower leg. The appearance of the skin was classified as follows: normal or smooth(-), rough(+), rough with minute scaling(++), rough with extensive scaling(+++). In the same areas the water content of the stratum corneum was measured with the Corneometer CM 420 (Schwartzhaupt, Medizintechnik GmbH, 5000 Köln 30). The surface of the Corneometer probe is a capacitor which is influenced by a change in the dielectrical constant of the material in contact with it. In the skin, water has by far the highest dielectrical constant and an increase in water content will increase the capacitance of the Corneometer. The values are given as arbitrary units (AU). Thus, a high value indicates a relatively high water content. The mean value of three recordings was used. The recording zone is considered to be the deeper part of the stratum corneum (55,56). The Corneometer is reckoned to give reliable and reproducible data comparable to other methods for measuring the water

*Table I*

| | | PATIENTS | | | | CONTROLS | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | *Age* | | | | *Age* | | |
| Paper | | n | mean | range | Male/Female | n | mean | range | Male/Female |
| I | | 29 | 60 | 27-75 | 14(10)/15(9) | | | | |
| II | | 28 | 59 | 30-77 | 15(15)/13(13) | | | | |
| III | a | 18 | 59 | 35-77 | 9(6)/9(7) | 10 | 41 | 20-50 | 1/9 |
| | b | 10 | 59 | 35-71 | 6(5)/4(2) | | | | |
| | c | 77 | 60 | 27-77 | 42(23/35(24) | | | | |
| IV | | 31 | 58 | 34-78 | 16(9)/15(10) | 12 | 53 | 34-75 | 7/5 |
| V | d | 26 | 58 | 27-76 | 13(9)/13(9) | 10 | 57 | 37-78 | 3/7 |
| | e | 23 | 59 | 33-73 | 14(9)/9(7) | 9 | 57 | 35-75 | 4/5 |
| | f | 2 | 58, 61 | | 1(0)/1(1) | 16 | 37 | 21-57 | 2/14 |
| VI | | 12 | 62 | 38-76 | 7(6)/5(3) | 15 | 35 | 24-56 | 7/8 |

a. Intracutaneous injection of PTH
b. Immunohistochemistry of PTH
c. Serum concentration of m-PTH
d. Itch and flare induced by histamine
e. Itch induced by histamine
f. Histamine tachyphylaxis

( ) = number of patients with pruritus

*Table II.* Underlying renal diseases

| Diagnosis | Pruritus | No pruritus |
|---|---|---|
| Chronic glomerulonephritis | 14 | 13 |
| Chronic pyelonephritis | 6 | 3 |
| Renal hypertensive disease | 5 | 3 |
| Diabetic nephropathy | 3 | 3 |
| Interstitial nephritis | 1 | - |
| SLE | 2 | - |
| Renal amyloidosis | 2 | - |
| Polycystic kidney disease | 5 | 5 |
| Renal dysplasia | - | 1 |
| Bilateral nephrectomy | 1 | - |
| Other | 2 | 1 |
| Uremia, etiology unknown | 6 | 1 |
| Total | 47 | 30 |

content of the horny layer in vivo (56,57). In a recent study the Corneometer was compared with the Skicon-100, which measures electrical conductance, and both methods correlated well, although the Corneometer was more accurate and more sensitive for recording decreased hydration (55).

## Parathyroid hormone (PTH) (I,III)

***Serum and suction blister concentrations***

Serum concentrations of PTH were determined by two commercially available radioimmunoassay (RIA) methods. The mid-region PTH assay, reference range 0.5-1.5 μg/ml (m-PTH, Cambridge Medical Diagnostics) is directed against fragment 53-68. Measurement of the entire PTH molecule was performed with the intact PTH 1-84 assay, reference range 10-55 pg/ml (Allegro, Nichols Institute Diagnostics).

In five patients, m-PTH 53-68 was determined in suction blister fluid. Blisters were produced on the abdomen under a continuous negative pressure of 200 mm Hg for 2-3 hours using the Dermovac suction blister device (58).

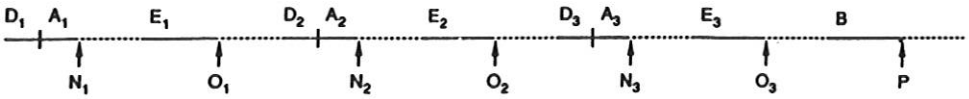


*Fig 1. Flowchart showing seven consecutive days comprising three dialysis sessions; $D_1$, $D_2$ and $D_3$. $A_1$, $A_2$ and $A_3$ = after dialysis sessions, the same day. $E_1$, $E_2$ and $E_3$ = days following dialysis. B = two days after dialysis. $N_1$, $N_2$ and $N_3$ = bedtime, dialysis days. $O_1$, $O_2$ and $O_3$ = bedtime, days following dialysis days. P = bedtime, two days after dialysis ——— = day, - - - - - - - - - = night.*

### *Intradermal injections*

Two fragments of the human PTH (hPTH) molecule, hPTH 1-34 and hPTH 44-68 were injected intradermally on the upper arms. Saline 0.9% was used as control. The biological activity of hPTH 1-34 had previously been demonstrated by U. Lerner, Department of Oral Pathology, University of Umeå, Sweden. Human PTH 1-34 was administered in concentrations between 100 and $10^{-4}$ ng/ml in 13 dialysis patients and 6 healthy controls and hPTH 44-68 in concentrations between 1000 and $10^{-4}$ ng/ml in 10 patients and 8 controls. The polypeptides were dissolved in buffered saline 0.9% and a volume of 0.01 ml was injected.

### *Biopsies*

Punch biopsies, 3 mm in diameter, were excised from glabrous skin of the fingertip. Lidocaine (0.5%) without epinephrine was used for local anesthesia. After immersion for 90 min in a solution of picric acid and formalin, the biopsies were rinsed for 24 h in 0.1 M Sörensen's buffer containing 10% sucrose, then sectioned at 14 µm on a cryostat and processed for indirect immunohistochemistry. The sections were incubated in the antiserum diluted 1:10, 1:100, 1:200, and 1:400 overnight, rinsed in phosphate buffer, then incubated for 30 min in tetramethylrhodamine-isothiocyanate isomer R (TRITC)- or fluorescein-isothiocyanate (FITC)-labelled antiserum, diluted 1:40 or 1:10 respectively. The following antibodies were used: Goat anti-PTH 1-84 and anti-PTH 1-34 (Nichols Institute), rabbit anti-PTH 44-68 (BioGenex) and anti-PTH35-84 (I.R.E.), chicken anti-PTH 1-34, anti-PTH 35-65 and anti-PTH 65-84 (INC). Fresh human parathyroid tissue obtained at operation was used as positive control.

## Intracutaneous histamine reactions (V)

Solutions of histamine (1.0, 3.3 and 10 µg/ml) in a volume of 0.01 ml were injected intradermally on the lateral aspect of the upper arms. The intensity of the histamine-induced itch was recorded continuously by the subjects, who were asked to move an indicator sliding along a 20 cm scale on a metal ruler. The indicator was attached to a potentiometer connected to an ink-writer out of sight of the subjects. By determining the area under the curve (AUC) we obtained a measure of the itch as a resultant of both duration and intensity. The area of the histamine-induced flare reaction was measured planimetrically 5 min after injection. In 26 dialysis patients, 18 with and 8 without pruritus, and 9 healthy controls, the itch intensity was recorded for a maximum of 5 min whereupon the area of the flare reaction was measured. In 23 dialysis patients, 16 with and and 7 without pruritus, and 9 healthy controls the itch intensity was recorded until it disappeared spontaneously.

In a parallel investigation we studied tachyphylaxis to histamine in 16 healthy controls and 2 dialysis patients. Histamine was repeatedly injected in the same spot at intervals of 90 min and 24h. Saline was used as control.

## Neuronal markers in uremic skin (VI)

Skin biopsies, 3 mm in diameter, were taken from the glabrous skin on the fingertip and from the lower leg in 12 dialysis patients and 15 healthy controls. The biopsies were processed for indirect immunohistochemistry (for details see above). The following antibodies were examined: neuron-specific enolase (NSE), neurofilament (NF), protein S-100, tyrosine hydroxylase (TH), myelin basic protein (MBP), substance P (SP), calcitonin gene-related peptide (CGRP), $\gamma$ -melanocyte-stimulating hormone ( $\gamma$ -MSH), somatostatin, galanin, thyrotropin releasing hormone (TRH), vasoactive intestinal polypeptide (VIP), peptide histidine isoleucine amide (PHI), neuropeptide tyrosin (NPY) and methionine-enkephalin (ENK).

## Statistical methods

Student's t test and the Mann-Whitney U-test for unpaired observations were used to test differences between mean serum concentrations (I,III).

Student's t test was incorrectly used to determine the duration of dialysis (I). The data were not normally distributed and recalculation using the Mann-Whitney U-test showed a tendency that patients with pruritus had been on hemodialysis longer than patients without pruritus (p=0.05)

Analysis of variance was applied in the evaluation of Pain-Track itch recordings (II) and stratum corneum water content measured by the Corneometer (IV).

The Kruskal-Wallis test and the Mann-Whitney U-test were used for evaluating cutaneous histamine reactions (V) and Wilcoxon's rank-sum test for the histamine tachyphylaxis data (V).

# Results and discussion

## Clinical aspects of uremic itching (I,II)

60-65% of the patients suffered from uremic itching, which tallies with previous observations in both hemodialysis and peritoneal dialysis patients (14,15,17). Clinical data regarding age, sex and underlying renal disease or routine laboratory analysis did not differ between patients with pruritus and those without.

Pruritic patients tended to have been on hemodialysis longer than non-pruritic patients ($p=0.05$). One could speculate whether this reflects a difference in residual renal capacity, either the glomerular filtration rate or some other as yet unknown renal function, which is liable to decline gradually in these patients.

Itching started before the initiation of dialysis in 13 of the 19 pruritic patients in study I and in 9 of the 28 pruritic patients in study II, but it was a manifestation of severe renal insufficiency appearing only shortly before active treatment became necessary.

Once established, pruritus seemed to persist. Of the 19 pruritic patients examined initially (I) only two who had undergone a successful renal transplantation were free of symptoms at the follow-up two years later, whereas another five of the ten non-pruritic patients had developed itching.

Itching could be generalized or localized. The main body sites affected by itch in 47 dialysis patients are presented in Table III. Evidently there are no definite predilection areas. The arm harbouring the fistula used for dialysis was affected relatively often, plausibly due to frequent washing and traumatization provoking itching. When patients were lying down during dialysis sessions and in bed at night symptoms were most pronounced on the back.

***Table III.*** Main areas affected by itch in 47 patients.

| Body site | Number of patients |
|---|---|
| General | 18 |
| Back | 13 |
| Dialysis arm | 9 |
| Face | 4 |
| Legs | 3 |

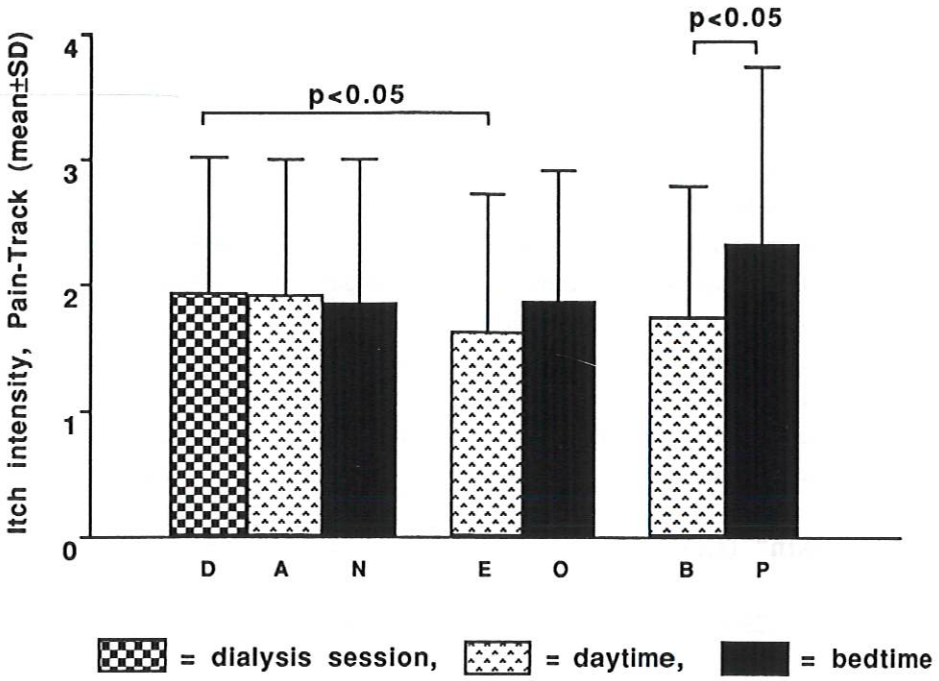


*Fig 2. Intensity of itch measured by Pain-Track in 19 patients. For symbols see Fig 1. D = $D_1+D_2+D_3$)/3. A = $(A_1+A_2+A_3)$/3. E = $(E_1+E_2+E_3)$/3. N = $(N_1+N_2+N_3)$/3. O = $(O_1+O_2+O_3)$/3. D>E ($p<0.05$). P>B ($p<0.05$)*

Questioning patients about fluctuations in itch intensity with special reference to dialysis sessions revealed no consistent pattern. There was poor concordance between patients' histories and the recording of itch intensity with Pain-Track and visual analogue scales (VAS). There was good correlation between Pain-Track and VAS, although statistically significant fluctuations were measured only with Pain-Track (Fig. 2). The main advantage of the Pain-Track compared to conventional visual analogue scales is the continuous surveillance of the authenticity of recordings. This will hopefully increase the reliability and sensitivity especially when measuring minor variations in symptoms, which was confirmed in our study. However, many patients found the Pain-Track bothersome to handle, which decreased compliance and restricted the duration of the investigation. Of the 28 patients 4 were excluded altogether and in another 7 patients single days were excluded due to lack of compliance.

Pain-Track recordings showed fluctuations of itch intensity in relation to dialysis treatment (Fig. 2) The highest day-time itch scores were assessed during dialysis sessions, which might suggest activation of pruritus due to treatment. Still, the perception of

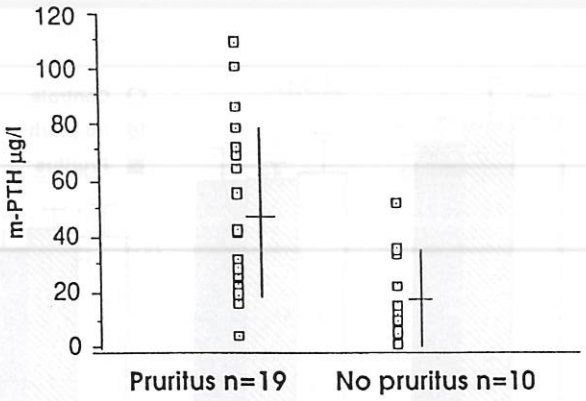


*Fig 4. Serum concentrations of m-PTH in 29 uremic patients with and without pruritus (mean±SD)*

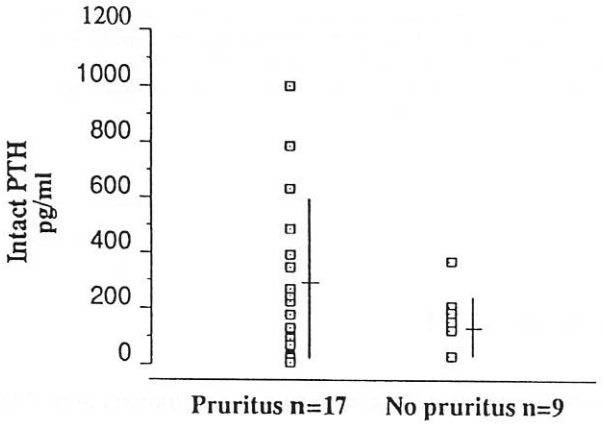


*Fig 5. Serum concentrations of intact PTH in 26 uremic patients with and without pruritus (mean±SD).*

pruritus has been discussed (61). Apart from regulation of the calcium-phosphorous homeostasis, other PTH-induced effects, such as vasodilatation, renin release and lipolysis(62-64) have been demonstrated. However, the possible physiological significance of these actions remains to be established. Besides increased secretion of PTH, uremic patients have an altered metabolism of the PTH molecule, accumulating "inactive" fragments with a slow turnover. Patients with primary hyperparathyroidism do not develop itching and it is notable that these patients as opposed to uremic patients, excrete PTH metabolites in a normal way. Thus, although biological activity has been demonstrated

solely for the amino terminal fragment of the PTH molecule (65), it seems justified to investigate possible pathogenic effects resulting from accumulation of other PTH fragments.

As a group, dialysis patients with pruritus have higher serum concentrations of PTH than patients without pruritus. This was evident when m-PTH was measured (our initial finding in 29 patients was later confirmed in 77 dialysis patients in study III), and when the intact PTH molecule was measured there was a definite trend. However, there was no correlation between the severity of pruritus and the serum level of PTH in individual patients (I).

If PTH were to act as a peripheral mediator of uremic itching, one might recover PTH in the skin. However, there was no evidence of accumulation of PTH in the skin, and the concentration of m-PTH in suction blister fluid paralleled the serum concentrations, probably only reflecting a transudation of PTH from serum (I). Immunohistochemical investigation using antibodies against different parts of the PTH molecule was negative (III). However, even though the antibodies stained fresh human parathyroid tissue obtained at operation, which was used as positive control, any antigen in the skin may not be accessible or may be of too low concentration for detection.

Intradermal injection of PTH fragments failed to evoke any acute or delayed cutaneous reaction. The concentrations injected covered a wide range, the highest much exceeding the serum levels encountered in dialysis patients. Hence, there was no indication of a pruritogenic effect induced by PTH itself. It has been reported that still higher doses of PTH induce mast cell degranulation (66,67), but in our investigation we could see no sign of histamine release.

In conclusion despite higher serum levels of PTH in dialysis patients with pruritus, our studies do not support a role for PTH as a peripheral mediator in uremic itching, and it could be speculated whether the accumulation of PTH in pruritic patients acts as a marker for some other pruritogenic substance. Still, a crucial question stays unanswered, namely whether the uremic itching originates in the peripheral or in the central nervous system. Theoretically either is equally conceivable, and the possibility of effects mediated centrally by PTH or other substances remains unexplored.

## Histamine reactivity (V)

### *Results*

Patients with pruritus had significantly stronger itch responses for all histamine concentrations than did patients without pruritus or healthy controls (Fig.6). There was no diffe-

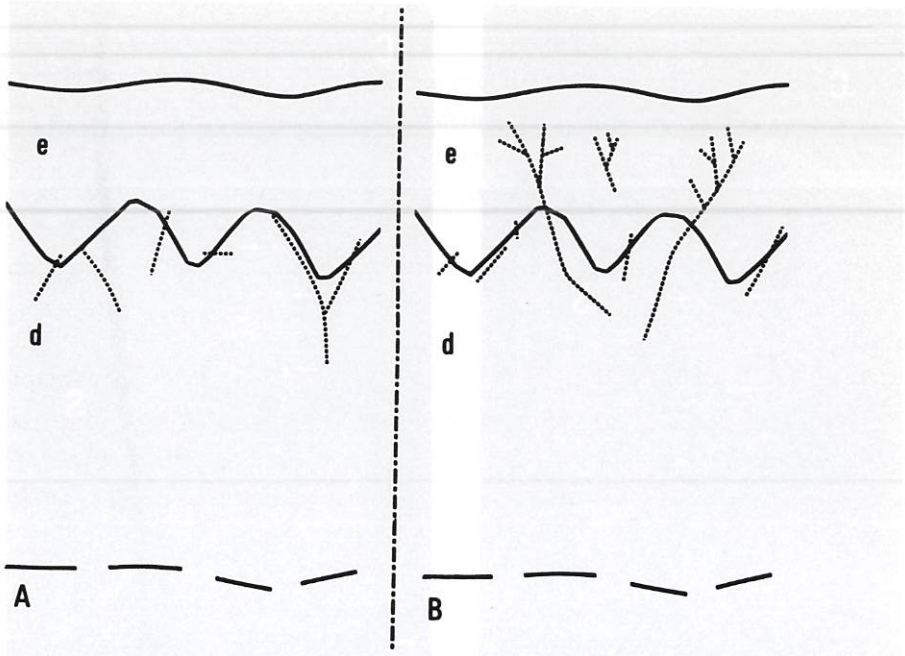


*Fig 9. Schematic presentation of the NSE-immunoreactive nerve fibers seen in normal (A) and uremic (B) human skin. In B, the nerve fibers are found sprouting throughout the epidermal layers, however, not penetrating the stratum lucidum, e, epidermis; d, dermis.*

dialysis patients without any sign of malignancy, and it was suggested that the finding was related to polyneuropathy in these patients (82). Whether the increased NSE levels mirror proliferation and sprouting of nerve fibers that might be associated with polyneuropathy (83) or reflect axonal degeneration and loss of nerve fibers occurring in uremic neuropathy (40), is an open question. Another explanation might be accumulation of NSE due to deficient excretion or impaired degradation.

# Principal Findings

Our study verifies a high frequency, 61-66%, of pruritus in patients undergoing maintenance hemodialysis. Patients with pruritus tended to have been on dialysis treatment longer than non-pruritic patients; otherwise there was no difference in clinical data or routine laboratory analysis between pruritic and non-pruritic patients.

The intensity of itching showed fluctuations with reference to dialysis sessions. Itching peaked at night after two days without dialysis, was relatively high during treatment and lowest during the day following dialysis. Our results suggest that the accumulation of pruritogens between dialysis sessions influences the itch intensity.

Most patients had dry-looking, xerotic skin. Measurement of the stratum corneum water content did not reveal any significant differences between dialysis patients as a group and controls. However, there was a tendency towards lower water content in patients with pruritus and a definite trend that clinically more xerotic skin areas were less hydrated.

In pruritic patients serum concentrations of m-PTH 53-68 were significantly higher than in non-pruritic patients. Measurement of intact PTH 1-84 showed the same tendency. However, in individual patients there was no correlation between the severity of symptoms and the PTH level. Intradermal injections of hPTH 1-34 and 44-68 did not evoke any cutaneous reaction. Histochemical investigation of uremic skin failed to detect any immunoreactivity for antibodies directed against different parts of the PTH molecule. Our results do not support PTH as a peripheral mediator of uremic itching.

Dialysis patients exhibited an abnormal response to intradermal histamine injections. Despite smaller flare reactions, patients with uremic pruritus perceived significantly more itching than patients without pruritus and controls. Tachyphylaxis to itch and flare after repeated histamine injections was demonstrated in both uremic patients and healthy subjects. The increased sensitivity to exogenously applied histamine in combination with the experimentally induced histamine tolerance rather seems to discredit histamine as the mediator of uremic itching.

NSE-immunoreactive thin nerve fibers were demonstrated sprouting throughout the layers of the epidermis in 12 dialysis patients but in none of 15 controls. Our results suggest that dialysis patients develop an abnormal pattern of cutaneous innervation.

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