Short Communications

001

Chronic Urticaria is Frequently Triggered by Focal, Particularly Gastrointestinal Infection: Analysis of 325 Cases

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We previously demonstrated a high frequency of *Helicobacter pylori* associated gastritis among 100 patients with chronic urticaria. Now, we carefully analysed 325 patients with chronic urticaria (mean duration of urticaria ± SD was 37.6 ± 60.7 months) attending our Department of Dermatology within 4.5 years. 65% were women, 47% had associated angioedema. In 21% additional physical triggering was found (11% dermographism, 4% cold urticaria, 3% cholinergic or delayed pressure urticaria each, 1% heat urticaria). 98/277 patients (35%) showed positive atopy screening (Sx1). In 18/141 patients (13%) elevated antibodies to thyroid were found, although thyroid function was normal. 30/325 patients (9%) gave evidence for pseudoallergic reactions triggering their urticaria.
In 207/325 patients (64%) a focal infection was identified by laboratory tests and/or special studies. In 135/207 (65%) gastrointestinal infections were found. 99/207 patients (48%) had *Helicobacter pylori* gastritis as assessed by ^{13}C-urea breath test and/or gastroscopy. 36/93 patients (39%) demonstrated abnormal yersinia-immunoblot. Intestinal candidosis was found in 80/200 patients (40%) whereas stool for O & P was always negative. Chronic ENT and dental focal infections were found in 28% and 22%, respectively. Other infections were present in 23/207 (11%). 51/325 patients (16%) were classified to have chronic idiopathic urticaria.
Taken together based upon our data obtained in 325 patients we propose a specific focal medical history and the assessment of at least *Helicobacter pylori* infection, yersiniosis, and streptococcal infections (ENT, dental) in the diagnostic management of chronic urticaria.

002

Sulfasalazine in the Treatment of Normocomplementemic Lymphocytic Urticarial Vasculitis

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The lymphocyte infiltration and wall vessel damage report about 20% of chronic urticaria outpatient. Clinically there are similar pattern to those without vasculitis lesion, but with a poor response to classic therapy. 70 urticaria vasculitis (UV) patients were selected into 4 pharmacological methodology during 12 weeks: Group I, 32 with sulfasalazine; Group II, 21 with methylprednisolone; Group III, 9 with dapsone; and Group IV, 8 with cetirizine. All the groups were evaluated to clinical symptoms and drug consumption each 2 weeks. The skin biopsies were also performed at the middle and at the end of the study. A washout period was done during 2 more weeks and after week 32. In a subsample of each group we also study cellular markers in skin histology (CD3, CD45RO, CD20, CD15).
We observed a complete clinical resolution in Group I patients, in 22 of 32 patients at week 2; 5 at week 3, 3 at week 4; and the other 2 with partial clinical control. Concerning histology 32 patients reverted to normal. In the final biopsy an increase in percentual CD45RO+ was observed (similar to that shown in normal skin) accompanied by a decrease in absolute number of CD3+ cells compared to the initial study. We also observed absence of CD15+ and CD20+ cells at the end of the trial. No clinical recurrence was present after sulfasalazine stopped.
From 21 patients of Group II, 5 presented clinical remission, 11 partial resolution, and no changes in other 5 patients. Only 4 patients showed normal histology at the end of the study. No clinical effectiveness were related in Group III and IV.
Our results showed a high efficacy of sulfasalazine on UV, with no side-effects and with modulatory cellular mechanism in the skin.

003

New Role for Mast Cell Tryptase in Cutaneous Inflammation: Protease-Activated Receptor-2 Regulates Inflammatory Responses in the Skin

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This paper reviews the recent knowledge about protease-activated receptor-2 (PAR2), a receptor for mast cell tryptase, and its role during inflammation. PAR2 is highly expressed in the skin of different species and can be detected in epithelial cells, endothelial cells, smooth muscle cells and various immunocompetent cells. Because tryptase has been shown to play an important role in mast-cell mediated diseases such as urticaria or allergic asthma, and this protease stimulates PAR2 in transfected cell lines, the aim of the study was to determine whether tryptase activates PAR2 in different cutaneous cells and may thus regulate inflammation. Moreover, since urticaria is well known to have a neurogenic inflammatory component, we tested whether tryptase mediates neurogenic inflammation in the skin via receptor-mediated activation of neuropeptide release from sensory neurons. Finally, regulation of PAR2-mediated cytokine release was measured in human dermal endothelial cells after stimulation with tryptase. PAR2-immunoreativity was detected in keratinocytes, endothelial cells, and dermal immune cells. PAR2 and tryptase are closely associated in various cells as shown by double immunofluorescence. Tryptase stimulates Ca-mobilisation in keratinocytes and dermal endothelial cells indicating this receptor is functional. In sensory neurons, PAR2 was detected in sensory neurons, and colocalizes with CGRP or SP. Tryptase and PAR2 agonists increased $[Ca^{2+}]_i$ in sensory neurons, and stimulated CGRP and SP release from sensory nerves. Intracutaneous injection of a PAR2 agonist caused marked oedema and recruitment of neutrophils that was abrogated by antagonists of CGRP type 1 and SP (neurokinin 1) receptors and by sensory denervation with capsaicin. Moreover, tryptase modulates cytokine release and expression of adhesion molecule expression in human dermal endothelial cells via PAR2. In conclusion, PAR2 agonists regulate cutaneous and inflammation by a neurogenic and non-neurogenic mechanism indicating that PAR2 plays an important role in inflammatory skin diseases such as urticaria.

004

Influenza A Virus Infection Induces Virus Specific Mast Cell Degranulation Leading to Local Anaphylaxis in BALB/c Mice

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A frequent clinical condition is the development of urticaria or allergic asthma following viral infection. It is currently unclear how viral infections, which usually lead to TH1 dominated immune responses, can mediate the development of allergic symptoms, which are thought to be a result of TH2 responses towards antigens. To address this question we infected BALB/c mice with influenza virus and 3 weeks later checked for influenza specific antibody responses, specific T-helper cell subsets and active cutaneous anaphylaxis after intracutaneous rechallenge with virus antigen. As expected, influenza infection lead to the induction of influenza specific T-helper 1 type cells secreting high amounts of IFN-γ but no detectable IL-4 or IL-5 after influenza antigen specific restimulation. In addition, high levels of specific antibodies of the IgG1, IgG2a and IgG2b subtype can be detected 3 weeks after influenza infection. Influenza specific IgE antibodies were found in very low levels. Interestingly influenza virus specific antibodies were relevant for eliciting allergic symptoms like active cutaneous anaphylaxis following intracutaneous virus antigen challenge. In conclusion we show here that virus antigen induces specific mast cell degranulation leading to local anaphylaxis in BALB/c mice. This provides a possible mechanism to explain infect associated exacerbation of atopic diseases like urticaria or asthma.

005

Conditions for Indirect Detection of Functional Auto-Antibodies to Anti-FceRIa: Basophil Histamine Release (BHR) Using Serum of Patients with Chronic Urticaria (CU)

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In 1/3 of patients with CU IgG antibodies (Ab) to the α-chain of the high affinity IgE-receptor (Anti-FcεRIα) have been demonstrated. Anti-FcεRIα-Ab are cross-reactive to tetanus toxoid and are not necessarily anaphylactogenic (*Eur J Immunol* 29:1139, 1999). Therefore, functional assays for the detection of crosslinking Ab might be superior compared to immunoassay-based determination. This study explores appropriate conditions for indirect Anti-FcεRIα-Ab detection by BHR. After dextrane sedimentation mixed leukocytes from selected donors ($BHR_{Anti\text{-}IgE}$–50% of total histamine) were washed twice before incubated for 40 min at 37°C. After centrifugation (15 min, 4°C, 700 × g) supernatants were carefully removed and analyzed fluometrically; cell pellets were disintegrated (2% $HClO_4$) and removed too (15 min, 4°C, 700 × g), enabling separation and subsequent detection of released and cellular (nonreleased) histamine to avoid serum artefacts. Serum (1:2–1:100 diluted) did not modify spontaneous or IgE-mediated BHR (n = 7) significantly. Screening 50 sera from CU patients, 11 showed dose-dependent BHR, reproduced with different basophil donors. Removal of basophilic IgE by lactic acid pretreatment to open IgE receptors induced a shift of BHR curves of selected sera to lower or higher concentrations, separating presumably Anti-FcεRIα-mediated from IgE-mediated stimuli. Serum pretreatment (56°C, 3 h) did not abolish BHR, except for one serum, most likely containing Anti-IgE-Ab. Preliminary experiments indicate that selected sera from CU-patients do not only induce BHR, but also dose dependent sulfido-leukotriene release (assay kindly provided by DPC Biermann) from IL-3 pretreated basophils. BHR might facilitate screening of sera for functional Anti-FcεRIα- or Anti-IgE-activity permitting further definition of their clinical relevance in patients with CU.

006

Is Extensive Clinical Examination Relevant for Chronic Urticaria? Results of an In-Patient Study at Kiel University

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Chronic urticaria presents a common, distressing and partly life-threatening disease. Until today, both pathogenic concepts and therapeutic regimens remain a medical challenge. Consequently, in individual cases, extensive search for underlying causes is initiated with often disappointing results. To evaluate serological and clinical markers, data from 339 in-patients with chronic urticaria treated at the Department of Dermatology of Kiel University from January 1994 to July 1997 were evaluated retrospectively. Apart from case-history, inflammatory, immune and infectious serological parameters, microbiological and hormonal parameters as well as results from clinical ANT, odontological, gynaecological and chest X-ray examinations were gathered. Furthermore, allergological *in vitro* and an vivo evaluation including oral provocation with food additives were included. Altogether, defined causes could be found in 16.8% of patients. Whereas *in vitro* parameters were only rarely changed, foci could be found in up to 50% of patients, presented mainly as tonsillitis and sinusitis. Physical causes were demonstrated in 31% of patients. In oral provocation, dyes and preservative agents account for 4.5% of positive reactions, 5.6% to salicylate and 0.9% to bisulfite. Consequently, extensive search for underlying causes must only follow detailed case history and initially orientating laboratory monitoring.

007

Retrospective Study on the Implementation of Guidelines for the Diagnosis of Chronic Urticaria and/or Angioedema

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In 1995 guidelines were introduced for the diagnosis of patients with chronic urticaria (Kozel MMA, Mekkes JR, Bossuyt PMM, Bos JD: The effectiveness of a history-based diagnostic approach in chronic urticaria and angioedema. *Arch Derm* 134:1575–1580, 1998). The centerpiece of this guideline is that extensive laboratory screenings should only be performed in particular cases, indicated by careful history-taking with the use of a standardized questionnaire. In this retrospective study we investigated the use and the benefit of these clinical guidelines.

We analyzed patients records of all patients who visited the outpatient Department of Dermatology during January 1998 and February 2000. In the 140 patients identified we investigated how often the questionnaire was used, how often routine laboratory tests were performed at the first visit, and on which information (history-taking, questionnaire, laboratory tests, provocation tests) the diagnosis was made.

In 71 patients (50.7%) a reason for the urticaria was found. In 63 of the 71 patients (89%) the cause of the urticaria was already suspected by history taking and in 8 patients (11%) the diagnosis was found by the questionnaire. 26 patients had urticaria factitia, the most common finding. In 48 patients the questionnaire was not in the patients file. In 89 of 140 patients (64%) extended laboratory tests, not based on history taking or the questionnaire, were requested at the first visit and this did not reveal the cause in any patient.

In this retrospective study the identification of a cause for urticaria in 50.7% is slightly higher than 45.9% of the prospective study. This may be partially explained by 10 patients (7%) with a contact urticaria to latex. With this study we confirmed the importance of history taking, the use of a questionnaire and the test for dermatographism in finding the cause of urticaria. Additionally, routine laboratory tests, even limited, did not help in finding the cause of urticaria.

008

Prevalence of Antibodies to the High-Affinity IgE Receptor in Chronic Urticaria

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Various etiopathogenic factors are suspected to result in the clinically rather homogenous picture of urticaria. Cross linkage of surface IgE receptors on mast cells by specific antigens is regarded as one distinct feature in the evolution of urticae. In addition, autoantibodies to the high affinity IgE receptor with histamine releasing activity have recently been demonstrated in a subset of chronic idiopathic urticaria. In the present study, the prelevance of such antibodies was further evaluated in a total number of 350 different sera from patients with acute, acute intermittent, chronic persistent and recidivating urticaria. The full-length extra-cellular part of the α-chain was expressed in the baculovirus system and used to detect antibodies of different sub- and isoptypes by Western blot analysis. In parallel, sera were evaluated for histamine releasing activity *in vitro*. IgG antibodies could be detected in 14–50% of sera with highest incidence in chronic idiopathic recidivating urticaria in contrast to only 25% of normal sera. Only a subset of sera were shown to induce histamine release *in vitro*. In such patients, immunosuppressive regimens directed to modulate pathogenetically relevant autoantibodies may be used successfully in addition to simple antihistamine treatment.

009

Demonstration of Histamine Releasing Autoantibodies in Chronic Idiopathic Urticaria by a Simplified Histamine Release Test

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Several studies have shown that 40–60% of patients with chronic idiopathic uticaria (CIU) have autoantibodies to IgE and/or its receptor and that these patients benefit from immunosuppressive treatment. Autoantibodies have been demonstrated by basophil histamine release which correlated to the severity of CIU. So far the widespread applications of these findings in the daily diagnosis of CIU has been limited by the restricted access to a basophil histamine release test. Based on a commercial assay (HR-Test, RefLab, Denmark) we have developed a simplified test for detecting histamine releasing activity. Serum from 76 individuals comprising controls and different forms of urticaria were tested including 27 patients with CIU. In brief 100 µl diluted serum samples (50, 25 and 12.5%) were incubated with 100 µl dextran-sedimented cells from one donor and a release of > 12% was considered positive. The results showed that 9 out of the 27 CIU patients with cholinergic urticaria were positive. Histamine release varied from serum to serum (range 15–65%) as well as the serum titer inducing a positive response (range 50–12.5%). The results were confirmed on basophils from two other donors. No patients with other forms of urticaria or healthy donors were tested positive. Our results suggest that the HR-Test may be of clinical value in identifying CIU patients who have developed histamine relasing autoantibodies probably binding to IgE and/or its receptor.

Posters

P01

Extra- and Intracellular Expression and Regulation of CXCR1 and CXCR2 in HMC-1 Cells and T-Lymphocytes

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In previous studies, we have described the expression of IL-8 and both types of IL-8 receptors, CXCR1 and CXCR2, in human skin mast cells and the mast cell line HMC-1. Besides extracellular we also demonstrated an intracellular expression of both receptor types. In order to investigate whether intracellular receptor expression is restricted to mast cells or is a more common phenomenon, we now extended our studies to T-lymphocytes and asked for the regulation of IL-8 receptor expression after cell stimulation. RT-PCR-analysis demonstrated the mRNA for CXCR1 and CXCR2 in HMC-1 and T-cells. Extracellular and intracellular protein expression of CXC-R1 and -R2 was demonstrated in both cell populations, HMC-1 showing the highest percentage. Surprisingly and in contrast to CXCR4, extracellular expression of CXCR1/R2 was down-regulated after stimulation with PMA and Ca-Ionophore. CXCR1 and CXCR2 showed different kinetics of down-regulation. Rapid internalization is the most likely explanation. Internalization may add to the constitutively expressed internal pool of IL-8 receptors. In further studies we want to investigate whether the intracellular pool contributes to the rapid reappearance of IL-8 receptors on the cell membrane as described for neutrophils after their stimulation.

P02

Chronic Urticaria and Angioedema in 140 Patients: a Retrospective Analysis

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Between 1993 and 1997, 258 patients had been investigated for chronic urticaria and/or angioedema. Using a standardized questionnaire in a telephone interview, 140 patients (87 women [64%], 53 men [36%]) were reassessed on the long-term course of their symptoms in spring 2000. In 37% of our patients the symptoms had cleared completely and in 36% there was marked improvement in the frequency of attacks. 22% reported on no difference and in 4% the disease had got even worse. Chronic tonsillitis diagnosed by clinical examination and/or an elevated antistreptolysin-titer was seen in 29 patients (21%); tonsillectomy was done on 15 patients, 8 of them being free of symptoms at follow-up. A diagnosis of sinusitis was made in 10 patients (7%); in only 1 of the 6 treated patients the symptoms were improved afterwards. Six months after treatment 48 of 49 patients with dental foci still complained of urticaria. Gastroscopic examination revealed chronic gastritis in 36 of 42 investigated patients (86% of all patients); 60% of them still suffered both from dyspepsia and urticaria when reassessed. Surprisingly, only in 10 patients *Helicobacter pylori* was detected by a urease test or histological examination of gastric mucosa. Unfortunately, eradication therapy was only documented in 2 cases, one of them being symptom free at follow-up. Milk and fruits were the two most often mentioned alimental triggers. 28% observed an adverse influence of nonsteroidal antiphlogistics. Of considerable interest is the high rate of atopic disposition in our population (45% of all patients). 47 of them (74%) still had urticaria at follow-up. Given the long duration of symptoms, it is not surprising that 56 patients asked for paramedical advice, which was found to be helpful by 20. In conclusion, urticaria and angioedema had completely resolved in 36%, and the frequency of attacks had significantly decreased in 37% at follow-up. Potential risk for a long-term course of urticaria/angioedema were: long duration of symptoms when first seen in hospital (in 49 of 89 patients still suffering from urticaria when reassessed; 55%), atopic disposition (in 47 of 89; 53%), gastrointestinal symptoms (in 52 of 89; 58%) and intolerance to certain food (in 43 of 89; 48%). Further studies on a possible role of anti-Fcε/IgE autoantibodies in our patients are in progress.

P03

Chronic Urticaria: *In Vivo* and *In Vitro* Evaluation of Autoimmune Etiology in 110 Patients

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The aim of our study was to evaluate the autoimmune etiology of chronic urticaria in 142 patients (pts) selected on the basis of negative tests for other forms of urticaria. Among them, 25% were atopic; adverse reactions to NSAIDs were reported by 41%; 47 was the mean age; the women to men ratio was 1.5:1. We carried out skin tests with autologous serum: blood was allowed to clot both at room temperature (''classic test'') and at 37°C (''variant test'') for one hour before centrifugation. Skin tests were evaluated according to Grattan (Grattan CE: Histamine-releasing autoantibodies in chronic urticaria. *Skin Pharmacol* 4 Suppl 1:64–70, 1991). Classic test yielded positive results in 59% of pts and 25% of healthy control subjects, while variant test was positive in 84% and 45%, respectively. Antinuclear autoantibodies were found in 14% of pts, antithyroid in 13%, anti gastric parietal cells in 10% and anti pancreatic island in 2%. *In vitro* histamine release from whole blood of healthy donors yielded positive results in 42% of pts with positive skin test (variant) and in 25% of controls. Studies of HLA class II aplotype revealed a statistically significant increase of prevalence of HLA DR 7 (20% vs. 12% of Italian population). In a two-years follow-up study concerning 70% of our pts, we observed that the majority had a good quality of life when treated with antihistamine therapy. Only 4 pts needed steroids and 2 patients Cyclosporin A.

Conclusion The prevalence of positive results of skin test with autologous serum was high, in particular using the variant test (clotting at 37°C); also in controls it was higher than expected. More research is needed to evaluate if the variant test is more sensitive or less specific, in particular comparing it with serologic tests for anti-IgE and/or anti-FcεRI Aab.

P04

Pathogenic Diagnostic Efficiency from Anamnesis and Laboratory Procedures in Chronic Urticaria

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Background Chronic urticaria (CU) lasts by definition for more than 6 weeks. Older series report an identifiable cause in only about 20% of cases (Champion RH, Roberts SO, Carpenter RG, Roger JH: Urticaria and angio-oedema. A review of 554 patients. *Br J Dermatol* 81:588–597, 1969). This figure has much improved and in other series chronic idiopathic urticaria (CIU) represents 45% (Doeglas HM: Reactions to aspirin and food additives in patients with chronic urticaria, including the physical urticarias. *Br J Dermatol* 93:135–144, 1975) or 60–70% (Illig L, Paul E: Internal causes of urticaria. *Verh Dtsch Ges Inn Med* 84:919–920, 1978).

Objective To assess the pathogenic diagnostic efficiency from the study protocol of CU at the Department of Dermatology, Hospital del Mar.

Material and Methods The first, non selected, 126 adult patients with CU visiting the Urticaria Unit were included in a prospective study. All patients were submitted to a detailed anamnesis. Laboratory procedures and provocation tests were performed in a protocolized way according to the anamnesic orientation. Among others: a complete study of thyroid autoimmunity, screening for infections including Helicobacter Pylori and search for autoimmune urticaria with autologous serum skin test were performed.

Results This study included 86 females and 40 males with CU (mean age 41.63±14.43 s.d. years old). 26.19% were physical urticaria and CIU represented 69.84%. Specific provocation test showed 14 dermographic, 13 cholinergic, 7 pressure, 3 solar, 2 afrigore and 2 true aquagenic urticaria. Clinical and pathologic findings of urticaria vasculitis were found in 5 (3.9%) patients. The most relevant finding to discuss are: 37.5% of patients showed IgE levels > 100 UI/ml, the incidence of autoimmune thyroid disease was higher than in general population (26.13%), 61.66% of patients showed a positive breath test or Helicobacter Pylori, autoimmune urticaria by positive autologous serum skin test was demonstrated in 34.14% of tested patients.

Conclusion The study protocol of CU allowed to find at least one aetiologic, pathogenic or promoting factor in 50% of patients. Most cases cleared with antihistamines but severe autoimmune urticaria needed and succesfully responded to immunomodulatory drugs.

P05

A Male Case of Adult Onset Mastocytosis with Relatively Rapid Spread of Mast Cells

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We present a male case of a systemic mast cells disease with pronounced skin involvement. In our patient, aged 53 years, who suffered from asthma for 30 years, skin lesions started to appear 5 years ago, first on the legs and subsequently the lesions spread all over the body including the face, head and dorsal aspects of the extremities. Skin lesions presented as extremely dark brown macules, which urticated relatively vaguely after rubbing (Darier's sign). Basic laboratory tests did not reveal any abnormalities. Histopathological examination from the lesions (Astra blue stain, Giemsa method and pinacyanol erythrosinate) confirmed clinical diagnosis of urticaria pigmentosa. In radiological examination tubero-fibrous lesions in the second segment of the upper lobe of the left lung were found (Tbc was excluded). This finding was confirmed by CT scan with some suggestion of the neoplastic process. Bone scintigraphy revealed some gatherings of the marker in both tarsal bones. This finding was confirmed by NMR suggesting some noninflammatory infiltrate. Bone marrow biopsy and trepanobiopsy revealed multinucleated gatherings of mast cells. Features of some dysplasia were noticed in the granulocyte system – mainly lack of granules in younger cells. The patient complained from considerable pruritus and was put on anti H1 antihistamines with quite good effect. For the present moment, the patient declined any invasive procedures and treatments which would not bring good permanent results.

P06

Topical Steroid Application under Wet Wrap Occlusion in Mastocytosis

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Eleven patients with mastocytosis were treated with topical fluticason propionate under wet wrap occlusion. The aim of this project was to study a new treatment strategy using topical steroids. The experimental design was case controlled. Each patient received two dilutions of fluticason propionate (10% and 25%) applied daily under a wet wrap occlusion dressing. The duration of the treatment was 6 weeks. The patients were evaluated at 3, 6, 12 and 24 weeks after the start of treatment. The evaluation consisted of repeated measurements of routine blood and urine analysis, including urine N-methylhistamine and serum cortisol. Clinical improvement was assessed using a semiquantative scoring of mastocytosis (SCORMA). Biopsies from the skin lesions were obtained, before and six weeks after treatment. A reduction in activity of the skin lesions, expressed as improvement in the scorma index, was observed in 9/11 cases. The number of cutaneous mast cells was reduced by 10–60% after treatment. However pigmentation was only reduced in a minority of the patients treated with wet wrap. It is concluded that wet wrap treatment for cutaneous mastocytosis may be an option for treating large skin surfaces especially in children. In adults the spectrum of treatment options is wider, still favourable results may be achieved using the wet wrap method.

P07

Comparison of Telangiectases and Mast Cells in Telangiectasia Macularis Eruptiva Perstans (TMEP) and Generalized Essential Telangiectasia (GET)

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Telangiectases (TE) are thought to occur through the release or activation of vasoactive mediators in association with numerous pathological conditions. TMEP is a clinical variant of mastocytosis, whereas GET is not associated with any underlying disease. Our objective was to elucidate differences in number, distribution, and phenotype of TE and mast cells (MC) in either condition. We investigated lesional biopsies from a 6-year-old-child with TMEP and a 40-year-old woman with GET as well as normal skin from two controls. Cryostat sections were stained by APAAP-technique with antibodies to the MC growth factor stem cell factor (SCF) and to the following MC markers: SCF receptor (c-kit), MC proteases tryptase and chymase, and FcεRI-α chain. To characterize TE, staining was done for collagen type IV, fibronectin, laminin, vs. Willebrand-factor, actin, desmin, CD31,HLA-DR, VEGF-R, and PDGF-R.

Results TE were larger, wider and located deeper in the dermis in GET, compared to TMEP. Vessel walls were positive for collagen type IV, fibronectin, laminin, CD31, and v. Willebrand-factor, and negative for actin, desmin, and PGDF-R in both conditions. HLA-DR and VEGF-R were positive on TE in TMEP only. In the upper dermis, SCF stained vessel walls in TMEP, but not in TE of the GET lesion. MC located in the vicinity of TE were lower in number in GET, compared to TMEP, as evidenced by only few c-Kit, tryptase, chymase, and FcåRI-positive MC close to TE in GET. The increase of mast cells in TMEP may be due to proteolytic cleavage and thus activation of SCF, with subsequent vessel growth due to the angiogenic action of VEGF and tryptase. For GET, an underlying MC-associated pathomechanism seems unlikely.

P08

Vibratory Angioedema and Pruritus

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Vibratory angioedema is a rarely mentioned subtype of physical urticaria first described in young adult patients working with a pneumatic hammer. However many patients describe pruritus following everyday vibratory stimuli like riding a bicycle over cobblestone pavement.

Since no data to the prevalence is available in the literature we have started a pilot study investigating by questionnaire a representative group of 81 medical students (mean age: 24 years, range: 22–37 years) attending the dermatology course.

In 9 of the participants with anamnestic vibratory angioedema and 6 control persons without these complaints we performed a provocation test by putting one palm on a vortex for 4 min Before, 5 and 15 min after the provocation blood sample was taken for the measurement of serum-histamine content from the draining vein. 22.2% of the participants of the questionnaire stated to have symptoms in the palms after vibratory stimuli. The main symptoms were pruritus (100%), urticae (16.7%) and angioedema (5.6%). Women were more frequently (2:1) afflicted. On provocation only participants with a positive history reacted with erythema and pruritus (100%), with angioedema of the hand (33.3%), and urticae (22.2%). Study participants with vibratory angioedema showed a significant ($p = 0.001$) increase of serum-histamine content after provocation in contrast to the control group without anamnestic vibratory angioedema.

Although only a small group was examined, it can be stated that the reaction to everyday vibratory stimuli is quite frequent in young adults. In the majority of people only pruritus or urticae occur instead of the originally described angioedema. This may be regarded as an abortive form since mast cells are clearly involved, which is shown in the increase of histamine.

P09

Detection of IgE Antibodies to *Helicobacter pylori* by Immuno-Blotting Technique

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The connection between chronic urticaria and *Helicobacter pylori* (*H. pylori*) has been under interest. We found in our earlier study elevated IgE levels in patients with chronic urticaria and especially in patients with *H. pylori* infection, and therefore we wanted to characterize the IgE inducing structures of *H. pylori*.

The cultured *H. pylori* was handled with 10 different ways to find the optimal antigen extract to be used in the IgE assays. Immunoblotting was used to detect the IgE binding bands. *H. pylori* RAST was carried out in 25 *H. pylori* infected and in 9 noninfected patients with chronic urticaria.

The largest number of IgE binding bands were found in extracts prepared from the washing fluids, while strong heating and denaturing treatments destroyed the epitopes for IgE binding suggesting that the antigens belonged to the flagellary structures of *H. pylori*. A pool of 2nd and 3rd washing fluid and a sonicated extract for 1.5 min after 3rd wash (1:1:2) was chosen to be used in *H. pylori* RAST-assay. In *H. pylori* RAST elevated levels of IgE antobodies to *H. pylori* was detected only in one of 25 *H. pylori* infected patients. All of the *H. pylori* negative patients remained negative.

Our results suggest that, although IgE binding bands were found against *H. pylori* in immunoblotting, the development of *H. pylori* specific IgE response is not common.

P10

***Helicobacter pylori* in Chronic Urticaria**

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Introduction Chronic urticaria (CU) can be defined as the occurrence of wheals on a daily or almost daily basis over a period longer than 6 weeks. The aim of this study was to determine the possible triggering factors of CU, and to define the importance of *Helicobacter pylori* in the etiology of CU.

Methods At the Allergy Unit of the Department of Dermatology and Venerology, Zagreb University Hospital Center, 154 patients with CU were recorded during a 3-year period (1996 to 1999). According to sex distribution, there were 112 female (72.7%) and 42 (27.3%) male patients, mean age 43 years. The diagnosis was based on careful clinical history and relevant laboratory findings. The infection with Helicobacter pylori was evaluated by commercial serologic tests, ELISA and complement fixation test which detect specific IgG antibodies, or by endoscopy with biopsy.

Results Focal infection as the possible eliciting factor of CU was found in 85 (52.59%) of 154 patients, mostly Candida spp in stool (n=36; 23.37%), parasitic infestation (n=12; 7.79%), and streptococcal pharyngitis (n=10; 6.49%). Concerning focal infections, serologic tests or endoscopy with biopsy revealed *Helicobacter pylori* in 14 (9.09%) patients. Thyroid autoimmunity and mental disorders were diagnosed in 4 (2.59%) patients each. Taken together, we identified a relevant etiopathologic factor of CU in 89 (57.79%) cases, whereas 65 (42.21%) patients were considered to suffer from idiopathic urticaria.

Conclusion CU is a frustrating problem for both the physician and patient. Serious disabilities of patients with CU are the loss of sleep and energy, social isolation, including altered emotional reactions and difficulties in some aspects of daily living. Thus, the search for possible etiopathogenetic factor is of great importance. The measurement of *Helicobacter pylori* specific antibodies or gastroscopy should always be included in the diagnostic procedure for chronic urticaria.

P11

***Helicobacter pylori* Specific Cellular Immune Response in Chronic Urticaria Patients**

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Chronic urticaria is a common skin disorder the cause of which is unknown in the majority of the cases. *Helicobacter pylori*, the most important etiologic factor of gastritis and peptic ulcer, has recently been associated with several extradigestive diseases. Previous studies have reported beneficial effects of *Helicobacter pylori* eradication on chronic urticaria, but contradictory results were also published. Peripheral blood mononuclear cells (PBMC) of 24 chronic idiopathic urticaria patients (13 seropositive/11 seronegative) and 18 healthy controls (9 seropositive/9 seronegative) were stimulated with whole heat-killed *Helicobacter pylori* (10^6–10^8 bacteria/well), mitogens PHA (2 μg/ml) and PWM (5 μg/ml). Helicobacter specific IgG antibody response was determined by commercially available enzyme linked immunosorbent assay (Varelisa). There were significantly higher proliferative responses both to whole heat-inactiveted *Helicobacter pylori* ($p = 0.015$) and PHA ($p = 0.007$) in 6–7 day cultures of peripheral blood mononuclear cell in chronic idiopathic urticaria patients than in healthy controls. We found a tendency to exhibit a higher proliferative response to Helicobacter antigens and mitogens in seropositive than in seronegative ones. Our results support that there is an increased T-cell reactivity in chronic idiopathic urticaria which is further enhanced in the presence of Helicobacter. *Helicobacter pylori* therefore plays a triggering role in the pathogenesis of chronic idiopathic urticaria.

P12

Parvovirus B19 in Chronic Urticaria Patients

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The aetiology of chronic urticaria (CU) is not known. However, in some cases infectious agents have been suggested as triggering factors. When a 16-year-old-male with a history of a recent parvovirus infection developed CU, the suspicion arose that parvovirus B19 could have a role in the development of his disease. Parvovirus B19 gene sequences were detected from a skin biopsy specimen of this patient. Thereafter, a more extensive study in 36 CU patients was done by amplification of parvovirus B19 sequences from skin samples using two sets of primers and a probe. Molecular amplification of the human β-globin was used as a methodologic control. B19 DNA was detected in 18/36 (50%) skin biopsy samples of the CU patients. Interestingly, 14/22 (64%) skin biopsy samples from healthy controls also harbored parvovirus B19 sequences. All 32 persons positive for B19 DNA had circulating IgG-class antibodies to B19 major structural protein VP2.

Conclusion Parvovirus B19 DNA is commonly detected in the human skin. Therefore, the association between parvovirus B19 infection and CU remains uncertain.

P13

Parasite-Induced Urticaria – Cases and Hints

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Parasites are frequently argued as a cause in urticaria, although according investigations often result negative. We present 2 cases of parasite-induced urticaria and give hints for a rational diagnostic procedure.

A 67-year-old-man presented with chronic intermittent urticaria and Quincke's oedema during the last 8 years, accompanied by lash-like urticarial flares visible for several hours. The main abnormal findings were blood eosinophilia (650 cells/ml) and highly elevated total IgE (2040), but a negative allergological investigation. On the other hand a positive EIA against *Strongyloides*-specific IgE and larvae of *Strongyloides stercoralis* in the stool were found. The parasite was possibly acquired in Brazil 9 years ago. The lash-like flares can retrospectively be interpreted as "larva currens" – a phenomenon typical for Strongyloidosis. Treatment with Albendazol (70 mg/day) for 10 days led to resolvement of the urticaria within a few months.

Also in a tropical area, a 38-year-old-man began to suffer from urticaria whenever in contact with cold water; a positive ice cube test proved the diagnosis of a cold-induced urticaria. Stool parasitology revealed a strong presence of *Giardia lamblia*. Under treatment with Tinidazol (2 g single dose) the cold urticaria resolved within a few days. 2 additional re-infestations with giardiasis were accompanied again by cold urticaria, also with rapid relief after antiparasitic treatment.

Urticaria due to parasites should be considered in all patients with a history of a tropical residency. Also intake of exotic food such as raw fish is a potential source of parasites known to cause urticaria (e.g. Anisakiasis; Gnathostomiasis). Marked blood eosinophilia and/or markedly elevated total IgE should in addition lead to a parasitological examination in urticaria patients.