the present study, we used TNFα deficient mouse (TNFαKO mouse) to investigate the role of TNFα in skin sensitization and CHS. We also studied on CHS in interleukin-1α/β (IL-1) deficient mouse (IL-1KO mouse). The efficiency of skin sensitization to 2,4,6-trinitrochlorbenzene (TNCB) measured 6 days later as a function of challenge-induced increases in ear thickness in IL-1KO mouse slightly diminished as compared with that in wild mouse. The ear thickness in TNFαKO mouse was about 47% of that in wild. Surprisingly, TNFαKO mouse was devoid of LC, which was stained with a monoclonal antibody against IAd in epidermis. However, draining lymph node cells (LNC) in TNFαKO 3 days after the treatment with 0.5% TNCB had almost the same ability to proliferate as that of LNC in wild. These results indicate that LC may not be necessary to establish skin sensitization step.

P2C33
Immunological alterations in blood of toluene diisocyanate-sensitized mice

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Immune functions are known to be sensitive to a variety of chemical exposures. Availability of immunologic biomarkers in blood to evaluate environmental risks was investigated in toluene diisocyanate (TDI)-sensitized mice. Selected immunologic indicators in blood were total and TDI-specific IgE levels in serum and cytokine mRNA levels and lymphocyte composition in blood cells. Female BALB/c mice were sensitized with TDI painted 3 times on dorsal skin. Three days after the last TDI exposure blood samples were collected and analyzed for specific IgE by ELISA and mRNA levels of IL-4 (Th2 cytokine) and IFN-γ (Th1 cytokine) by RT-PCR analysis. Results showed that TDI exposure produced no changes in lymphocyte subpopulations like T, B, CD4 + and CD8 + cells in spite of reduction of WBC numbers in blood. However, it significantly increased both total and TDI-specific IgE levels as compared to controls. Correspondingly the exposure also definitely induced IL-4 mRNA levels but suppressed IFN-RNA levels in blood cells, despite considerable variation in individuals. In conclusion our findings indicate that Th2 dominant status caused by TDI was confirmed from alterations in IgE levels and cytokine balance in blood, and those blood immunologic biomarkers would be applicable to risk evaluation in human population.

P2C34
Modulation of the IgE reponse to natural rubber latex proteins by glutaraldehyde

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Latex allergic health care workers are exposed to numerous chemicals in addition to natural rubber latex (NRL) proteins. Time course studies have demonstrated a dose responsive increase in total and NRL specific serum IgE levels in female BALB/c mice exposed to 25 μg NRL and increasing concentrations of glutaraldehyde from 0.05ppm — 1% (doses surrounding the recommended PEL). These studies investigated the mechanistic basis underlying the immunomodulation of the IgE response to NRL proteins following concurrent glutaraldehyde exposure. Using in vitro flow through cells and skin from hairless guinea pigs, penetration studies demonstrated no significant increases in NRL protein penetration through skin from animals that had been exposed dermally to 0.75 ppm glutaraldehyde 5 days a week for up to 56 days. Immunohistochemical staining of epidermal sheets demonstrated up regulation of MHC class II expression following 3 days of exposure to glutaraldehyde. No significant increase in MHC class II expression was observed in lymph node cells from animals exposed to NRL alone. Ten days following co-exposure to glutaraldehyde and NRL proteins, an increase in MHC class II expression (> 45%) was observed in lymph node cells draining the site of exposure. Draining lymph node cells demonstrated no exposure related changes in CD23 expression, however, a significant increase in the percent of CD40 + cells was observed in mice exposed to NRL proteins alone or concurrently with glutaraldehyde. These studies suggest that the observed immunomodulation by glutaraldehyde does not result from an increase in the dermal penetration of NRL proteins, but glutaraldehyde may enhance antigen presentation and B cell activation.

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P2C35
Evaluation of the potential for dermal exposure to 3-Amino-5-mercapto-1,2,4-triazole (AMT) to induce pulmonary hyperreactivity

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3-Amino-5-mercapto-1,2,4-triazole (AMT) is an intermediate in the production of the herbicide DE498. Little toxicological information is available for either compound. These studies were conducted, using BALB/c female mice, to evaluate the potential of AMT to cause allergic sensitization and induce pulmonary hyper-reactivity following dermal exposure. Using the Local Lymph Node assay, AMT was identified as a sensitizer at concentrations of 15% and greater. AMT was negative for contact sensitization in the Mouse Ear Swelling Test. Phenotypic analysis of draining lymph node cells following 4 days of dermal exposure demonstrated an increase in B220 + cells at all concentrations of AMT tested and a significant increase in IgE + /B220 + cells in the 25% dose group. In sub-chronic

dermal exposure (5 days a week for 11 weeks) studies, 4 of 5 animals exposed to 25% AMT had elevated levels of total serum IgE and 2 of the 5 experienced airway hyperreactivity upon methacholine challenge. Cytokine modulation in draining lymph node cells was determined by RNase Protection Assay. Upregulation of cytokines associated with TH2 responses and mast cell growth and differentiation (IL-4, 5, 10, 13, and 9) was observed. These studies suggest that AMT is a sensitizer with the potential to induce pulmonary reactivity.

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P2C36

Deletion of glutathione *S*-transferase theta-1 (GSTT1) and anti-convulsant (ACD)—induced hypersensitivity syndrome

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The use of phenytoin (PHT) and carbamazepine (CBZ) is associated with the development of hypersensitivity reactions in 5–10% of patients. Cytochrome P450-dependent metabolism of these drugs may result in the formation of reactive intermediates, drug-protein adducts and the initiation of drug-induced autoimmune reactions. GSTs are critical enzymes in the conjugation and subsequent detoxification of electrophilic metabolites. We hypothesised that a genetic deletion of polymorphic GSTT1 may be a risk factor in the development of ACD-induced hypersensitivity. Using a PCR-based approach, we genotyped hypersensitive patients and control subjects for GSTT1 and GSTM1. Of the patient group 3/8 (38%) and 5/8 (63%) were null for GSTT1 and GSTM1, respectively, while 1/27 (4%) and 14/27 (52%) control subjects were null for GSTT1 and GSTM1, respectively. Using a one-tailed Fisher's exact test, the proportion of patients with the GSTT1 defect was found to be significantly higher ($P < 0.05$) than that of control subjects. These results suggest that a deletion of GSTT1 may be associated with the occurrence of PHT- or CBZ-induced hypersensitivity reactions.

P2C37

Are oils used as laxatives in cosmetics or skin care a trigger for arthritis?

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The objective of this study was to assess the pathogenic potential of oils, used cosmetically/taken internally, by their capacity to induce chronic polyarthritis in rats. Arthritis development was quantified 11–15 days after a single tailbase inoculation of admixtures of test oils with either an (a) auto-antigen = collagen type II (C-II), emulsified with an oil and 2.5% Arlacel, given intradermally into Wistar rats; or (b) exogenous arthritigen = heat-killed *Mycobact. tuberculosis* (MT) for intralymphatic (subdermal) inoculation into Dark Agouti rats. Significant polyarthritis was induced by admixtures of oil with arthritigen: oils or arthritigen alone being non-toxic. Administering MT (in saline) and oil alone at separate sites in the tail also induced arthritis. Combinations of C-II and MT were synergistic when admixed with cosmetic oils. Notable intoxicants were products sold as 'baby'/bath oils (mineral oil, apricot kernel), 'facial'/'skin'/'body' oils (soya bean, persic, macademia nut), up-market cosmetics (jojoba bean, avocado) and 'moisturisers' e.g. Sorbolene (mineral oil-water emulsion). By contrast, oils used externally in two cultures with low incidence of rheumatoid arthritis, namely emu and goanna oils (Australian Aborigines), ngali nut oil (Solomon Islanders) were non-toxic. In conclusion, oils accepted as harmless may become toxic when external barriers (gut, skin) are breached allowing undigested oils to stimulate Langerhans (skin) and other immunoreactive cells. Rheumatoid arthritis, a relatively modern disease, may be associated with (i) increasing use of oily emollients applied to skin, scalp; (ii) consumption of mineral oil laxatives; and (iii) using mineral (baby) oils for infants' nappy rash.

P2C38

Evaluation of the safety limits and potential toxicity of chlorinated drinking water in rats; immunobiochemical and ultrastructural study

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Recently, studies have been attempted to evaluate the risks associated with a lifetime exposure to chlorinated drinking water, where it has been reported to impair some immune functions. The present study aims to investigate the safety limits and the potential immunotoxic effects of chlorinated drinking water. In this study, 56 adult male albino rats were used. Animals were divided into seven equal groups ($n = 8$), one control and three groups were treated with sodium hypochlorite at different concentrations 2, 15, 30 parts per million, and the remaining three groups were also treated with monochloramine at concentrations 2, 15, 30 parts per million, respectively for 3 months. For each animal, body weight, spleen weight per body weight ratio, phagocytic function of peritoneal macrophages, electron microscopic study of splenic macrophages, lymphocyte blastogenesis and interleukin-2 were investigated. Results showed that the body weight was not significantly affected, while the spleen weight/body weight ratio was significantly decreased. Also, phagocytic function of peritoneal macrophages, lymphocyte blastogenesis and interleukin-2 were significantly decreased. Electron microscopic examination of the splenic macrophages showed high activation at the lowest concentration 2 parts per million, while higher concentrations 15 and 30 parts per million showed different degrees of suppression, reaching its maximal effect at the highest concentration. These changes could be attributed to the toxic effects of the chlorine byproducts on the immune system.

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Abstracts

Lectures

Deichmann Lecture
Apoptosis and toxicology — What relevance?

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All cells are mortal — i.e. they can be killed if a vital metabolic process is blocked. All cells can engage in a variety of stress responses, such as the heat shock response, when vital processes are slowly, or only partially, inhibited. These stress responses involve detection of the damage, transduction of signals, and activation of a response, such as production of heat shock proteins, proteases, or chaperones. Many cells possess mechanisms whose purpose is to kill the cell. Such physiological cell death mechanisms are used to remove unwanted or damaged cells. Among metazoans, physiological cell death is implemented by a family of cysteine proteases, termed caspases, that exist in a latent state even in healthy cells. Cells killing themselves via activation of their caspases typically exhibit an appearance termed 'apoptosis'. Apoptosis is not only used to remove cells in physiological circumstances, such as during development, but is also a common response to cell stress. Thus many cells will detect damage to, or malfunctioning of, vital metabolic processes, and generate signals that lead to activation of the caspases, and apoptotic death of the cell. This has led to a great deal of confusion, because many drugs and toxins with known biochemical functions have been found to induce apoptosis, and rather than this being interpreted as a stress response, it has often wrongly been assumed that apoptosis is a direct effect of the drug or toxin.

Plenary Lectures

L1
The pathogenesis of prion diseases

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Prion diseases occur because the full length prion protein (PrP) can exist in two conformations: (1) a normal conformation in which the N-terminal half of the molecule has little or no β-sheet, which is characteristic of PrPc; and (2) an abnormal, pathogenic conformation in which the N-terminal half acquires a β-sheet conformation, which is characteristic of PrPSc in scrapie and bovine spongiform encephalopathy (BSE) of animals and Creutzfeldt-Jakob disease (CJD) in humans. The property of the prion protein which gives prion diseases the characteristics of a slow virus infection is the efficient conversion of PrPC into nascent PrPSc when the former physically interacts with 'infecting' PrPSc. Sporadic CJD accounts for 85% of human prion diseases and appears to be initiated by the spontaneous conversion of PrPC to PrPSc (a one per million event). Familial CJD (15%) is caused by mutations of the PRNP gene. The PrPSc in sporadic and familial CJD is infectious. Prion strains are defined by the disease phenotype they produce in a host animal. Conformational dependent immunoassays indicate that the PrPSc comprising each prion strain has a different conformation, possibly as a result of different amounts of β-sheet and different PrPSc polymerization patterns. All of the parameters that define each prion strain can be modified by manipulating the amino acid sequence of PrP, which supports the protein only hypothesis. Finally, neuronal dysfunction and death in prion diseases require both the conversion of PrPC to PrPSc and the accumulation of nascent PrPSc in or on neurons and their processes.

L2
Food and cancer

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Food is an important factor in determining cancer incidence in many countries and regions. Food components relevant to cancer development can be divided into macro- and microcomponents. The former tends to act indirectly. The latter usually has a clearly defined action, for example as genotoxic agents. Food can have both positive (carcinogenic) and nega-

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