

# INA Newsletter

International Neurotoxicology Association

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## President's Message:

Report from a visit to Szeged

On May 17-20, 1996 I visited Illes Desi and his team in Szeged to discuss essentials for the forthcoming INA6 meeting. Upon returning from this informative visit I am enthusiastic concerning the success of INA6, although the funding situation needs improvement. INA6 will take place 29 June - 4 July, 1997. Let me summarise facts and impressions as follows:

**Location:** Szeged is a medium sized university city (ca. 180000 inhabitants) beautifully located on the banks of the broad Tisza river (river Theia). It is a green city with parks and trees and has a distinct southern almost Mediterranean charm with many open air restaurants and bars, and many young people around. When I was there it was hot and humid, in July it is supposed to be hot and dry. The train connection from Budapest (West station) is convenient (55 Dollars 1st class round trip) and takes only 2-21/2 hours.

**Accommodation and conference venue:** Most of the conference participants will be accommodated in the elegant, three star spa hotel "Forras" where the conference takes place as well; it is located at only 10 min walking distance from downtown Szeged. Rooms range from elegant single (with sunny balcony) to standard three bed rooms (no balcony), each equipped with telephone, TV, bathroom and toilet. We agreed on reduced prices ranging from 215 (single), 145 (double) to 83 (triple) US-Dollars/person for five nights including buffet-style breakfast. Conference facilities are excellent. The hotel offers a variety of health-promoting facilities including tennis court, swimming pool, sauna, body building, but also inexpensive medical care (stomatology, plastic surgery, dermatology, internal check-up). In addition to this accommodation a limited number of student rooms

are available at 10 Dollars/person (3 person apartments) for five nights in downtown Szeged.

**Scientific programme:** Here we are almost suffering from an embarrassment of riches. Proposals range from "Neuroimmunology and Neurotoxicology", "Polymorphisms in Neurotoxicology", "Neurotoxicology of Al or Cd", to "Neurotoxicology in Eastern and Central Europe", to name just some of the proposals. It will be the task of the programme committee to select, shape and decide, taking the external funding situation into account; a lot still needs to be done in this respect. Fixed elements of any programme are (1) the Jacob Hooisma Lecture, (2) a debating session on "testing vs understanding", and (4) poster sessions. A programme committee has been proposed but still needs EC-approval.

**Registration fee and social programme:** We agreed on a graded registration fee ranging from 250 US-Dollars for senior scientists from US and EU-countries (full programme), 80 Dollars for senior scientists from former socialist countries, 70 Dollars for students/graduates (US and EU), and 30 Dollars for students/graduates (former socialist countries). The social programme includes (1) get-together-party, (2) conference dinner with music, (3) an excursion to the Hungarian Puszta. An accompanying persons' programme and post-congress tours will be prepared.

**Additional entertainment:** The revenge soccer game INA-Italy vs INA-Rest of the World is on the agenda. Music is on the agenda as well, since Hungary is not only the country of gypsy-music but also the country of Bela Bartok and Zoltan Kodaly. We propose that active INA-musicians organise a performance at INA6. Those of you who used to play or still play an instrument are kindly requested to contact me briefly describing their skills and interests (classic, jazz, string quartet, Haydn etc.). I will then try to structure a programme. This is unlikely to become

professional but should be fun. I am looking forward to hearing from you.

Gerhard Winneke, President, INA.

## **A database framework for selective neurotoxic lesions - a spin-off from recent developments in gene expression atlas projects**

[The following article by Ed Conley, author of the *Ion Channel Facts Books* tells of an interesting opportunity for neurotoxicologists to take part in the developing information revolution in neuroscience. We are already familiar with protein sequences being "published" on computer networks, and now we may have an opportunity for our findings about selective neurotoxicity to be integrated with basic neuroscience information about brain protein topography and function - Editor].

There is great current interest in establishing networked databases capable of recording processes of differential gene expression in brain. These resources are considered indispensable to archive and retrieve the extraordinarily complex spatio-temporal patterns of gene and protein interactions one observes in the brain. Patterns of expression are generally related to brain function by means of a linked functional / anatomical atlas. Highly restricted gene expression patterns infer a selective role in brain, as opposed to a ubiquitous 'housekeeping' function. Part of the argument used for such 'databasing' is increased accessibility by the scientific community and the capacity to generate 'searchable' data-sets based on selective criteria of interest. For example, the latter might ask "where does the expression of receptor A overlap with ion channel B?". Such differential gene expression patterns can then be used to formulate hypotheses, predicting a receptor-channel coupling which may be tested by direct experiment.

Like gene expression patterns, there appears to be several good reasons for considering compilation of selective neurotoxic lesion data within a database framework: (i) Accessibility - comprehensive studies describing selective lesions could be archived within the database and described using annotation tools; querying of such databases would generally be via a simple, universally-accessible WWW front-end. (ii) Interpretability - as for gene expression databases, there is great added value if different studies can be compared directly within

the same database framework. (iii) Developmental neurotoxicity - selectivity of neurotoxic lesion implies a differential sensitivity which may be a function of developmental lineage. Some gene expression database software would be capable of examining patterns of neurotoxic lesions during embryonic development, thus being able to critically analyse the relationship between neuronal death and cell lineage in the developing brain. This information, when combined with selective gene expression data from the same co-ordinate set may provide new insights into the mechanisms of selective neurotoxicity.

It would be valuable at this stage to compile a list of neurotoxic 'phenotypes' which show striking selectivity as they may be amenable to analysis in a brain gene expression database. Over the long term, it would be of some interest to further analyse these patterns of selectivity in terms of differential gene expression patterns that may exist in brain regions, subsets of neurones or individual nuclei. While presently this appears to be a 'needle in a haystack' problem, the developmental phenotype inferred by selective neuronal damage may lead to candidate mechanisms of toxicity in those cells.

Readers with examples of highly-selective neurotoxicity to contribute may send them via David Ray, or directly to Ed Conley on e-mail [ecc@le.ac.uk](mailto:ecc@le.ac.uk); FAX +44 116 2 5255586. In relation to the ion channel gene expression database project, readers may be interested in the Leicester Ion Channel Network web site beginning in October on <http://www.le.ac.uk/csn>, where further references to computer-based atlases for gene expression can be found.

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## **False Positives and the Demise of Neurotoxicology**

The advent of computers in toxicology has allowed investigators to collect large amounts of data and to analyse them with relative ease, but this event has also promoted the multiplicity of  $p$  values. Even though there is nothing wrong with

collecting lots of data in an exploratory mode, the results should only be used to generate more focused hypotheses rather than to draw any conclusions from such a study. Unfortunately, the literature is full of exploratory data that have been reported as hypothesis confirming rather than as hypothesis generating. As a consequence, a number of positive findings (too many) published in the scientific literature are simply the result of an uncontrolled Type I error rate ( $\alpha$ ) rather than the expression of a true effect.

Such a concern is not new (Sterling, 1959), and it may have been best expressed by Muller *et al.* (1984) who wrote: "If type I error rates for the experiments were unacceptably high and toxic effects absent, several experiments will have resulted in type I errors. It is quite likely that the type I errors will have been published, while the experiments with no significant results will not have been published. An illusion of well established toxicity may result" (p. 124).

When the number of derived  $p$  values increases, the overall Type I error rate can quickly become exceedingly high. When (i) the Type I error rate is controlled per comparison ( $\alpha_c$ ) and (ii) there are no correlations between the variables being assessed (i.e. independent measures), the overall likelihood that at least one significant test was obtained by chance can be calculated as

$$\alpha_{\text{overall}} = 1 - (1 - \alpha_c)^n$$

where  $n$  equals the total number of  $p$  values. For example, if  $\alpha_c$  is set at 0.05 and 10  $p$  values are derived ( $n = 10$ ),  $\alpha_{\text{overall}} = 0.64$ . As some degree of correlation usually exists in biological data sets, we can only conclude that the probability of generating at least one false positive is comprised somewhere between 0.05 and 0.64. The lower the correlation among variables, the higher the chance of at least one false positive. A reader's conclusion would obviously be different if 3 statistically significant  $p$  values were to be derived from a total pool of 3  $p$  values rather than of 100  $p$  values

Finally, it should be remembered that  $p$  values are to some extent a reflection of sample size, and that extremely low  $p$  values can be associated with very low strengths of association (e.g.,  $R^2$ ,  $\eta^2$ ), i.e. a very weak (but highly statistically significant) relationship may exist between independent and dependent variables. It is therefore recommended that one should provide the reader with some index

of strength of association besides  $p$  values (Kennedy, 1970).

In conclusion, a few steps would help alleviate the problem of false declarations of effects linked to the multiplicity of  $p$  values and would put the reader in a better position to evaluate the true strength of the data:

- researchers should be extremely selective in deciding which variable should be statistically evaluated in a hypothesis testing study;
- the investigator should not leave the reader under the impression that the study is a hypothesis testing enterprise when it is a hypothesis generating endeavour;
- the total number of derived  $p$  values (significant or not) should be identified;
- exact  $p$  values should be stated (e.g.,  $p = 0.013$  rather than  $p < 0.05$ );

If neurotoxicologists do not show some self-discipline and honesty, if they resist a reasonable request to share their data with other scientists, they will contribute to a distorted view of the true neurotoxicity of chemicals and will impede the progress of scientific knowledge.

#### References

- Kennedy, J. J. The eta coefficient in complex ANOVA designs. *Educational and Psychological Measurement* 1970, **30**: 885-889.
- Muller, K., Barton, C. N. and Benignus, V. A. Recommendations for appropriate statistical practice in toxicologic experiments. *Neurotoxicol.* 1984, **5**: 113-126.
- Sterling, T. D. Publication decisions and their possible effects on inferences drawn from tests of significance - or vice versa. *J. Amer. Stat. Assoc.* 1959, **54**: 30-34.

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[Hopefully we will respond to this helpful advice, and avoid selective presentation of our data. A sceptical attitude to one's own results is even more important than a sceptical attitude in a review of someone else's data - although rather harder to sustain! A further reference which may be useful is Muller, KE & Benignus, VA (1992) Increasing scientific power with statistical power. *Neurotox. Teratol.* **14**:211-219. - Editor]



The time of the next meeting draws nearer, and this is a reminder of some important dates and deadlines for your diaries:

Last date for registration & payment	15/1/97
Deadline for abstract submission	15/2/97
Date for abstract acceptance	1/4/97
Last date for 85% refund of payment	15/5/97
Meeting itself	29/6 - 4/7/97

Abstracts are to be submitted in camera ready form on an A4 or US letter sheet with a 4 cm top margin and 2.5 cm side margins. Typing should be clear (laser or new ribbon) in 12 point, single spaced. Start with the title in capital letters, a blank line, the initials and names of authors, with the presenting author first. Then give a blank line, and the address(es) of the authors, followed by a further blank line. The main text should be about 20 lines long, with no indentations, underlining, bold or italic print, with no graphs or figures. The length of the whole abstract should not exceed 12.5 cm. Any references should be included in the text.

For all other information see the attached registration forms, or ask Professor Desi direct.

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Would anyone like to suggest why the meeting hotel at Szeged might consider that neurotoxicologists would find a plastic surgery facility attractive? Look out for someone who may offer you a new face and a new identity in South America in return for providing them with secret information about the truth behind INA! Alternatively, if you hear a curiously familiar lecture given by a speaker that you do not think that have not seen before - check with the hotel surgeon!

- Editor.

**Copy for newsletter** by December please for January issue to David Ray, MRC Toxicology Unit, Lancaster Road, Leicester LE1 9HN, UK; fax: +116 252 5616; email: der2@le.ac.uk. You are invited to send personal news, events, details of meetings, titles of new theses, reviews, comments, jokes, abuse or anything else of interest to INA members.

# FINAL REGISTRATION FORM

(please use block letters or typewriter)

FILL IN THIS FORM ALSO IF YOU HAVE FILLED IN THE PREVIOUS ONE

## PARTICIPANT:

Family name:.....First name(s):.....

Affiliation:.....

Mailing address:.....

City:.....Postal code:.....Country:.....

Phone:.....Fax:.....e-mail:.....

I wish to participate ( )      I wish to present a poster ( )      I wish to hold a lecture ( )

ACCOMPANYING PERSON(S):.....

## REGISTRATION FEES:

Participants	250 USD	.....
Participants from East Europe*	80 USD	.....
Students**	70 USD	.....
Students from East Europe	30 USD	.....
Accompanying persons	125 USD	.....

\* valid only for participants from the previous socialist countries

\*\* for regular and PhD students only with a proper certificate from their institutions

Registration subtotal: .....

## ACCOMMODATION:

Please, indicate the type of room you wish. See the separate Accommodation Form for price and details.

### Hotel Forrás:

ordinary single room, incl. breakfast ( )      ordinary double room, incl. breakfast ( )

mansard single room, incl. breakfast ( )      mansard double room, incl. breakfast ( )

mansard triple room, incl. breakfast ( )

### Students' hostel:

triple room without breakfast ( )

## SOCIAL PROGRAM:

I am interested in the following social programs:

Daytime programs for accompanying persons ( )

Trip to the Hungarian countryside ( )

This form is for registration only and should be returned, until the 15th of December 1996, to Prof. Illés Dési to the address below:

Department of Public Health

Szent-Györgyi Albert Medical University; H-6720 Szeged, Dóm tér 10., Hungary

Phone: +36-63-455-119, Fax: +36-62-455-120

EMail: des@puhe.szote.u-szeged.hu

For final hotel reservation and for payment of registration fee and accommodation, use the separate form. Deadline for payment is the 1st of April, 1997.

# HOTEL ACCOMMODATION AND PAYMENT FORM

(Please use block letters or typewriter. Do not forget to sign the form below.)

## PARTICIPANT:

Family name:..... First name(s):.....  
Affiliation:.....  
Mailing address:.....  
City:..... Postal code:..... Country:.....  
Phone:..... Fax:..... e-mail:.....  
ACCOMPANYING PERSON(S):.....

REGISTRATION FEES:                      Subtotal from the registration form: .....

## ACCOMMODATION:

Rooms will be provided at Hotel Forrás, the congress venue. Additionally, a limited number of students' hostel 3-bed rooms will be available.

For double and triple, persons to share the same room:.....

Hotel Forrás:	ordinary single room, incl. breakfast, 5 nights:	215 USD	.....
Hotel Forrás:	ordinary double room, incl. breakfast, 5 nights:	145 USD/pers.	.....
Hotel Forrás:	mansard single room, incl. breakfast, 5 nights:	150 USD	.....
Hotel Forrás:	mansard double room, incl. breakfast, 5 nights:	110 USD/pers.	.....
Hotel Forrás:	mansard triple room, incl. breakfast, 5 nights:	83 USD/pers.	.....

Students' hostel: triple room without breakfast, 5 nights:                      10 USD/pers. ....

Accommodation subtotal: .....

Total amount: .....

## MODE OF PAYMENT (tick the one you use):

Bank transfer: Please, transfer the total amount, not later than 15th January, 1997, to the following bank account:

POSTABANK RT BUDAPEST HUNGARY, PAR AVION UTAZÁSI IRODA SZEGED,  
SWIFT CODE: POSB-HUHB 026-18232

Enclose a photocopy of the bank transfer receipt to this form.

Credit card:                      VISA:( )                      ECMC ( )                      AmEx ( )

Card No.:..... Expiry date:..... Holder's signature:.....

In cash on the spot: Only participants from East Europe (see Registration Form) who are not able to make a bank transfer can, exceptionally, pay on the spot..

This form must be returned to Prof. Illés Dési, not later than 15th January, 1997, to the address below:

Department of Public Health  
Szent-Györgyi Albert Medical University; H-6720 Szeged, Dóm tér 10., Hungary  
Phone: +36-63-455-119, Fax: +36-62-455-120  
e-mail: des@puhe.szote.u-szeged.hu

REIMBURSEMENT, with a 15% deduction, is possible until 15th April.

Date:.....

Signature:.....