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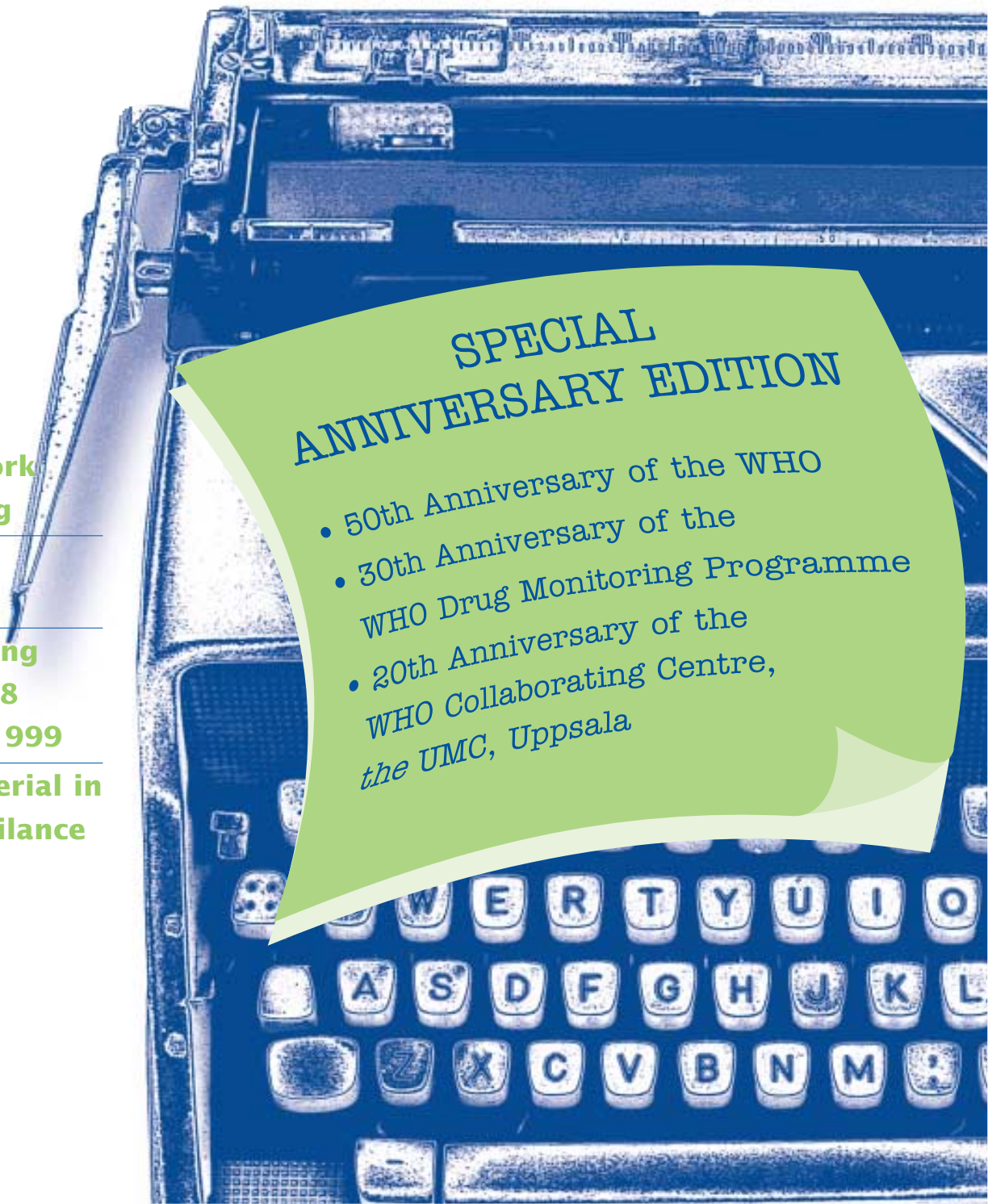
Uppsala reports

For everyone concerned with the issues of pharmacovigilance and toxicovigilance



SPECIAL ANNIVERSARY EDITION

- 50th Anniversary of the WHO
- 30th Anniversary of the WHO Drug Monitoring Programme
- 20th Anniversary of the WHO Collaborating Centre, *the* UMC, Uppsala

Welcome to Stockholm!

To those of you joining us for the Anniversary Symposium, a warm welcome to Sweden and to our meeting. We hope you will have a productive and very enjoyable time in this beautiful part of the world.

VÄLKOMMEN!

To the rest of our friends around the world, seasonal greetings and good wishes.

Message from
RALPH EDWARDS, DIRECTOR

This edition of *Uppsala Reports* is published to coincide with our Anniversary Symposium, taking place in Stockholm. It's an occasion to welcome personally many of our friends and colleagues from around the world and to extend our good wishes to those many more who will not be able to join us.

While there is much to celebrate in the achievements of the years since the start of the WHO programme, we're not going to spend much of our time looking back: the Symposium will be taking a very serious look at where we are now and where we should be heading for the future.

The Socratic Debate we shall be holding, takes as its starting point, our view that scientifically we still have a long way to go: the ideal position in relation to understanding the true balance of benefits and risks of drugs and in maximising drug safety is still elusive. So, we shall be debating the strengths and weaknesses of what we do now, in the hope of discovering significant new ways forward.

The timing of the debate is perfect: the WHO is currently discussing the future of the Programme and we at *the* UMC are reviewing our future strategy. It's a chance for everyone with an interest in the field to contribute actively, whether or not they are attending the Symposium. May I warmly invite you all to let us know your thoughts about how we can move strongly and positively forward.

Certainly we have achieved much, but I hope you will agree with me that anniversaries are very good times to plan for the achievements of the future.

With thanks and good wishes.

I Ralph Edwards

NEWS FROM *the* UPPSALA MONITORING CENTRE

Training material now available

the UMC has been contracted by the WHO Office for the Eastern Mediterranean (EMRO) to develop a programme and training material in pharmacovigilance. It is designed as a three day seminar for health professionals and staff at regulatory authorities interested in setting up a system for spontaneous reporting of ADRs.

This training programme was completed and tested for the first time in October this year in Morocco. The programme is made up of lectures, group discussions and descriptions of country models. It covers subjects from definitions, the rationale for pharmacovigilance, methods for setting up a pharmacovigilance centre, to case assessment, signal generation, evaluation and communication. Each section provides a set of transparencies with material for further reading.

The ambition of *the* UMC is to continue developing this training material and to adapt it to the needs of different regions, for example to provide translations into languages other than English. We intend to transfer the overhead projector material to computerized media and later on provide support for self-studies and distance training.

More information about the present training material and how to obtain it is available from Sten Olsson at *the* UMC.

New design of internet site

We recently redesigned our internet site to make it more informative and attractive. We are also setting aside more resources to update the site continuously and to make more documents and services available through the internet. Do visit it some time and follow its dynamic development! The URL is http://www.who-umc.org.

ESCOP symposium

The 5th International ESCOP (European Scientific Cooperative on Phytotherapy) symposium on Phytomedicine and Consumer Protection was held in London on 15th-16th October 1998.

The Symposium brought together drug regulators with leading scientists in the field who addressed the impact of the use of herbs on public health. It was an essential meeting for those involved in manufacturing, prescribing, and supplying herbal medicinal products.

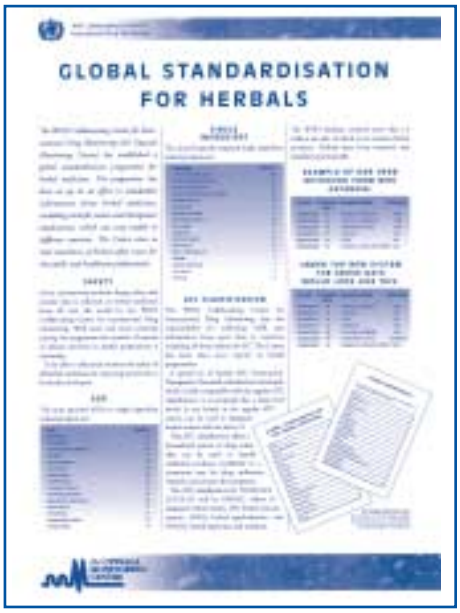
Among the leading topics was Key Issues in Herbal Pharmacovigilance presented by Ralph Edwards of *the* Uppsala Monitoring Centre. Ralph Edwards underlined the need for herbal classification by using the binomial names of herbals in order to avoid confusion caused by the use of only common names. Mohamed Farah of *the* UMC presented a poster with the title Global Standardization for Herbals which was one of five selected for an award as best poster. Please contact us at *the* UMC if you would like a copy of this poster.

Malin Ståhl

Dictionaries News

The current computerized versions of the Drug Dictionary, the Adverse Reaction Terminology and DD Access, professional version, now contain information up to and including the third quarter of 1998. The next versions, containing information for the fourth quarter of 1998, are expected to be available in February/March next year.

From November 1, DD Access, professional and standard versions, as well as ART Access will be available on CD-ROM instead of diskettes.



Mohamed's Poster

The Dictionaries Users' Group Meeting

Our Users' Group meeting was held for the second time this year. This time we met at the DIA Clinical Data Management meeting in Berlin, Germany, on October 26. If you wish to receive minutes from the meeting please contact us or visit our home page where you will find them.

(http://www.who-umc.org/meetings.html#WHODRUG)

Signal Development Project Questionnaire is now out

As mentioned in the previous issue of Uppsala Reports, there is a working group for reviewing the signal detection and evaluation process at *the* UMC. This group has put together a questionnaire in order to find out the needs of member countries and clinical experts before we implement any major changes in this area. The draft questionnaire was tested in one of the working groups at the Tokyo meeting of national centres. After considering the valuable comments we received from this group, we have now finalised the questionnaire and distributed it to all national centres and expert reviewers. If you have not received this questionnaire, please contact Malin Ståhl at *the* UMC as quickly as possible so we can send it to you. Your feedback on the questions we have is very important for our work and our service to you. We therefore respectfully ask you to respond to the questionnaire and return it to us as quickly as possible.

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Integrated Terminology Services (ITS)

Integrated Terminology Services (ITS) is a completely new approach to managing terminologies. It is a collaborative service provided by Chrystal Software, Virtual Hyper Glossary (VHG), WHO and *the* Uppsala Monitoring Centre (UMC). Chrystal Software has developed Astoria that manages the components of documents, particularly structured terminologies, based on eXtensible Markup Language (XML), enabled by VHG technology. Astoria's Web Services allows you to search and view using your usual internet web browsers. *the* UMC provides the medical terminologies, including the WHO Adverse Reaction Terminology and the International Classification of Disease from WHO.

ITS enables enhanced management of knowledge and service with the following benefits:-

- A single master copy for medical terminologies
- Easy navigation between terms, definitions and classification hierarchies
- Remote lookup of the latest terms
- Computer-aided coding
- Simple translations between languages (equivalent linguistic terms)
- No need to download recent dictionary updates unless you want to
- Retrospective chronological searches can find previous versions of terminologies
- Inherent difficulties in paper indexes such as alphabetical indexes are overcome
- Controlled language, lexical variants, spelling, second-guessing medical terms
- Easy annotate and review
- Run as a separate and supporting service or integrated into your existing systems
- Based on world wide web protocols, the service is platform independent, using existing internet browsers
- Internal intranet services mean that companies give free access to their internal terminological resources.

We are seeking partners for alpha testing and feedback. ITS is holding an open week giving access to web services in the near future.The dates will be provided separately as they are decided. Phone Anna Lindquist (+46-18 65 60 60) or e-mail : anna.lindquist@who.pharmasoft.se if you would like to be involved in the testing.

COURSES & MEETINGS
in PHARMACOVIGILANCE

■ **Management Forum** is organizing a basic training course in pharmacovigilance in London, 14-16 December 1998

For more **information** please contact:
The Management Forum
Tel: +44-1483-570099
Fax: +44-1483-536424
E-mail: management_forum@psilink.co.uk

■ **Henry Stewart Conference Studies** is organizing a conference on *Contra-indications - Avoiding Pitfalls and Solving Problems in the Management of Pre- and Post-Marketing Safety Assessment* in London, UK, 15 December 1998

For more **information** please contact the organizer:
Tel: +44-171-4043040
Fax: +44-171-4042081
E-mail: douvalt@henrystewart.demon.co.uk

■ **ARME-Pharmacovigilance** is having its 10th anniversary congerss in Bordeaux, France 19-20 January, 1999. The theme is *Evaluation of Drug Risks.*

For more **information** please contact:
Véronique Gigou
Hôpital Pellegrin, Bordeaux
Tel: +33-5-57571561
Fax: +33-5-56981291
E-mail: arme-p@pharmaco.u-bordeaux2.fr

■ The **Drug Information Association** (DIA) is holding the following workshops and courses in the drug safety area

- *Research and Regulatory Advances in Drug Safety*
  Toronto, Canada,1-2 February 1999
- *Safety Communications*
  Philadelphia, USA, 8-10 February 1999
- *Adverse Drug Reactions*
  Washington DC, USA, 22-24 February 1999
- *Drug Safety Surveillance and Epidemiology*
  Philadelphia, USA, 1-3 March 1999

For more **information** please contact:
DIA
Tel: +1-215-6282288
Fax: +1-215-6411229
E-mail: dia@diahome.org

■ The European Society of Pharmacovigilance (**ESOP**) will have its 7th Annual Meeting in Ankara, Turkey, 23-24 September 1999, following the meeting of representatives of national centres participating in the WHO Programme.

For more **information** please contact:
Ms Sevgi Öksüz
Tel: +90-312-2301674
Fax: +90-312-2301610
E-mail: tadmer@iegm.gov.tr

TIME TO ACT, INSTEAD OF TIME TO REACT

RECENT PUBLICATIONS

Opinion & Evidence Drug Safety

Guest editor of this new book, published by Adis International, is Ralph Edwards of *the* UMC who has also written the introductory chapter. The content of the book is based on material published in the periodicals *Drug Safety* and *Reactions*. It includes summaries of key reviews in drug safety written by international experts, concise summaries of original papers from July 1997 onwards and an A to Z listing of over 2000 significant case reports over the last year.
More information is available from:
Adis International Publications, Tel: +852-25110633,
Fax: +852- 25075554, http://www.adis.com

Nuevas Perspectivas de la Farmacovigilancia en España y en la Unión Europea

This book reviews the current perspectives on pharmacovigilance in The European Union as well as in Spain. Several topics are included in the ten chapters: from experience of the Spanish Pharmacovigilance System to new approaches to epidemiological databases and new information technologies in pharmacovigilance.

Thirteen annexes contain the European and Spanish regulations on pharmacovigilance as well as the Spanish translation of 3 ICH Guidelines (E2a, E2b, E2c).

For more information contact: Dr. Mariano Madurga, Co-ordinator of Spanish Pharmacovigilance System, Instituto de Salud Carlos III, E-28220-Majadahonda, Madrid, Spain, Fax: +34-91-5097948, E-mail: fvigilan@isciii.es; mmadurga@isciii.es

Drugs in Pregnancy and Lactation - A Reference Guide to Fetal and Neonatal Risk

The fifth edition of this standard textbook by Briggs, Freeman and Yaffe was recently published by Williams & Wilkins. It can now also be obtained on CD-ROM and updates can be subscribed to.
For information contact the publisher on:
Tel: +1-800-6380672, Fax: +1-800-4478438
E-mail: custserv@wwilkins.com

Benefit - Risk Balance for Marketed Drugs: Evaluating Safety Signals

This is the final report of the CIOMS Working Group IV on Drug Safety. It examines the theoretical and practical aspects of how to determine whether a potentially major, new safety signal signifies a shift, calling for significant action, in the established relationship between benefits and risks; it also provides guidance for deciding what options for action should be considered and on the process of decision-making should such action be required.
The book is available from WHO, Distribution and Sales, 1211 Geneva 27, Switzerland. Fax: +44-22-7914857, E-mail: publications@who.ch

An article entitled *Consumer protection and herbal remedies* by Mohamed Farah of *the* UMC appeared in WHO Drug Information vol 12(3), 141 - 142, 1998. Please contact *the* Uppsala Monitoring Centre for copies of the paper.

Neural Network Early Warnings

The decision to remove drugs from the market may have been strongly influenced by the negative publicity caused by the discovery of adverse drug reactions associated with them. We at *the* Uppsala Monitoring Centre attempt to highlight signals as early as possible so that pharmaceutical companies and regulators have as much time and information as possible to make the best decision about the use of a drug product.

To fulfill the mission more effectively we have developed a methodology for drug adverse reaction signal detection using a Bayesian Confidence Propagation Neural Network (BCPNN). This new methodology has given us a tool to discover signals very early.

By using the BCPNN we will obtain useful indications of possible side effects at an earlier stage, which will provide the opportunity to further investigate the potential problem and minimise the potential of unnecessary drug withdrawals. We believe that this data-mining approach will help those involved in drug safety make better risk assessment, labelling decisions on specific substances and, in general, facilitate a more flexible response to ADRs.


Mats Persson

According to our results described in the paper 'A Bayesian neural network method for adverse drug reaction signal generation'* and the test runs on market withdrawals in Sweden over the last couple of years, we would have been able to detect, with this new technique some signals 4-6 years before they were commonly recognised as signals.

We are in the process of introducing the BCPNN into our signal review process and the output will be provided to participating National Centres in the WHO programme. At the same time we will invite the pharmaceutical industry to subscribe to these new services: companies will be able to get information on their own products which have been highlighted by the neural network, so that they will be able to investigate the information themselves. Industry representatives will also be able to receive on a subscription basis any associated information relating to their own products, published in the Signal document, that is signals which have been highlighted as particularly important by our clinical experts.

The neural network approach will also allow us to perform complex variable analysis, leading to a better understanding of the high-risk groups of patients for specific drugs.

We feel that providing this information to industry as well as regulators will help to bring the key players together in the area of communication and drug safety.

We wish to provide you with time: 'time to act, instead of time to react' and look forward to your involvement in the project.

*A. Bate, M. Lindquist, I.R. Edwards, S. Olsson, R. Orre, A. Lanser, R. M. De Freitas. A Bayesian neural network method for adverse drug reaction signal generation. Eur J Clin Pharmacol (1998) 54: 315 - 321

News from Around the World

MALAYSIA

An international pharmacovigilance seminar, entitled *Drug Safety And You*, was organized jointly by Ministry of Health and WHO in Kuala Lumpur 13-16 October, 1998. The event attracted an audience of around 170 health professionals from all over Malaysia and representatives from neighbouring countries Thailand, Singapore, Brunei Darussalam, Laos, Indonesia, the Philippines and Australia. WHO was represented by Martijn ten Ham and Tokuo Yoshida and *the* Uppsala Monitoring Centre by Sten Olsson. At the seminar the internet home page of the Malaysian Adverse Reactions Advisory Committee (MADRAC) was inaugurated by the Malaysian Minister of Health, Mr. Chua Jui Meng. The URL of the homepage is http://www3.jaring.my/madrac/index.htm

Minister of Health, Malaysia and Martijn ten Ham

Sten Olsson and Minister of Health, Morocco

MOROCCO

The WHO Office for the Eastern Mediterranean Region (EMRO) contracted *the* Uppsala Monitoring Centre to develop a programme and training material for a three day training workshop to be carried out in the region. This training was carried out for the first time in Rabat 16-18 October 1998 with participants from Cyprus, Egypt, Iran, Jordan, Lebanon, Libya, Morocco, Oman, Pakistan, Saudia Arabia, Sudan, Syria, Tunisia and Yemen. The programme consisted of lectures by Sten Olsson and Ronnie Meyboom representing *the* UMC and working-group discussions. Country presentations provided inspiration for fruitful discussions on the role of pharmacovigilance in a national health care system. The Moroccan national pharmacovigilance centre, under the direction of Dr Rachida Soulaymani-Bencheikh, provided excellent facilities for professional as well as cultural and social activities.

ZIMBABWE

A sub-regional training seminar on pharmacovigilance was organized by the Medicines Control Authority of Zimbabwe in Kadoma Conference Centre, 3-6 August 1998. The seminar was attended by 29 people, including representatives from Botswana, Ethiopia, Lesotho, Kenya, Malawi, Mauritius, South Africa, Swaziland, Uganda and Zimbabwe. The event was sponsored by WHO Headquarters, Geneva, represented at the seminar by Dr Martijn ten Ham, and *the* Uppsala Monitoring Centre. The objectives of the seminar were to:

- introduce the concept of adverse drug reaction monitoring
- introduce guidelines on establishing pharmacovigilance centres,

and to provide training on

- how to promote reporting
- case report assessment
- tools for recording of report data

News from Around the World

INDIA

The Department of Clinical Pharmacology, at Seth G.S. Medical College, Mumbai (Bombay) has taken the initiative to set up a club for practicing physicians to encourage their active participation in drug monitoring activities. Professor N.A. Kshirsagar, head of the department, describes the idea as follows:

> *The SEM club membership idea originated from a need to encourage physicians who report ADRs to be given adequate feedback. The club also emphasizes the use of safe and effective medications. It was felt that the prescribing doctors are in need of information on medication-related issues.*

The function of the SEM club is as follows:

- Club membership
  Any physician can become a member of SEM club by filling in a questionnaire on a specific drug related reaction sent to them. Up to now we have sent two such questionnaires to 1000 and 350 physicians respectively with approximately 100 and 25 replies in each case. Letter and questionnaire are sent by post. Respondents will automatically become our members. Subsequent letters will describe the membership objectives and benefits in detail to encourage and assist in all activities.
- Club objective
  ~Safe and effective medication.
- Membership benefits
  ~Drug information and advice is provided free of charge by the department. A medical information service has been started. It has Medline up-to-date and access to the internet. It is open during office hours and is staffed by a pharmacist and a clinical pharmacologist. This was inaugurated on 1 October 1998.
  ~Referral and investigations on priority: we receive referrals for drug related issues routinely. Priority will be given to club members.
  ~Publication co-authorship. The first paper which will be submitted to the Lancet is entitled *Penalties of polytherapy: Mefloquine - Fluoroquinolone combination leading to convulsion.* Co-authors are Gogtay NJ, Manglvedhekar SS, Wagh VR, Waran MS & Mane D.
  ~SEM newsletter to be started. We need input from WHO and other colleagues around the world, informing us of drug alerts and ADRs reported from other countries.

If you wish to know more about the club idea please contact Professor Kshirsagar at Seth G.S: Medical College & K.E.M. Hospital, Parel, Mumbai 400 012, India. Tel : +91-22-4143505, Fax : +91-22-4143435, E-mail: dclphkem@bom5.vsnl.net.in

PORTUGAL

INFARMED has set up an internet home page at http://www.infarmed.pt. The site gives information on INFARMED's various services, publications and activities as well as listings of Portuguese medicines and pharmacies. In addition, ADR reports can be transmitted and INFARMED staff contacted directly, through the home page.

NEW ZEALAND

Dr John Fountain has joined the Committee on Adverse Reaction Monitoring (CARM) as the new Medical Assessor. He is in charge of the spontaneous reporting scheme. He continues to work half-time at the National Poisons and Hazardous Chemicals Information Centre. He is assisted at CARM by Dr Ruth Ferguson whose main task is to review and research adverse reaction reports. Director of CARM is Dr David Coulter who continues to run the Intensive Medicines Monitoring Programme.

The citadel of Ankara, Turkey

The next annual meeting of National Centres will be held in Ankara, Turkey. Details are given overleaf.

Obituary

~

Dr Susan Wood

Dr Susan Wood, Director of the Post-Licensing Division of the UK's Medicines Control Agency, died on 30 September, aged 46.

Born in Swaziland, she graduated in pharmacology with first class honours from King's College, London in 1973, and four years later qualified as a physician. In those early years she researched and published extensively in endocrinology.

In 1983 she began her career as a public servant with the Department of Health and had senior responsibility for adverse reaction monitoring in the UK from 1988. Then, and as Director from 1994, she radically overhauled the British system, implementing, among much else, the ADROIT computer system for handling ADR reports, and was Principal Assessor for the Committee on Safety of Medicines. She was involved in CIOMS, ICH, and the creation of MEDDRA. She was one of the two British representatives on the EU's Committee for Proprietary Medicinal Products, and chaired its pharmacovigilance working party.

She is credited with major influence in the field of drug safety in Britain and across Europe and was described by Dr Keith Jones, Chief Executive of the MCA as the 'supreme public servant.'

She is survived by her physician husband, John.

The WHO Drug Monitoring Programme

Annual meeting 1998 in Tokyo

The 21st annual meeting of representatives of national pharmacovigilance centres was held in Tokyo 7-10 September 1998. Representatives from 45 countries attended. The meeting was chaired by Dr Murray Lumpkin, USA with Dr Kenneth Hartigan-Go, the Philippines, serving as co-chairman. Ms Abida Haq, Malaysia and Dr Anthony Wong, Brazil served as rapporteurs. The programme included sessions on methods for signal generation, communications in pharmacovigilance, training activities, quality of reports, as well as discussions on individual drug safety issues. Representatives of newcomer countries in the WHO Drug Monitoring Programme presented their activities. A report from the meeting is available to national centres from WHO, Drug Management and Policy, Geneva.

Representatives of member countries met in Toyko, September 1998

Annual meeting 1999 in Ankara

At the Tokyo meeting Ms Sevgi Öksüz invited all representatives of national centres to come to the 1999 annual meeting to be held in Ankara, Turkey, 20-22 September. This meeting will be followed by the annual meeting of ESOP, the European Society of Pharmacovigilance, also in Ankara.

the Uppsala Team

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Manager (Research & Development):	Marie Lindquist
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	Malin Ståhl *(Biomedical)*
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