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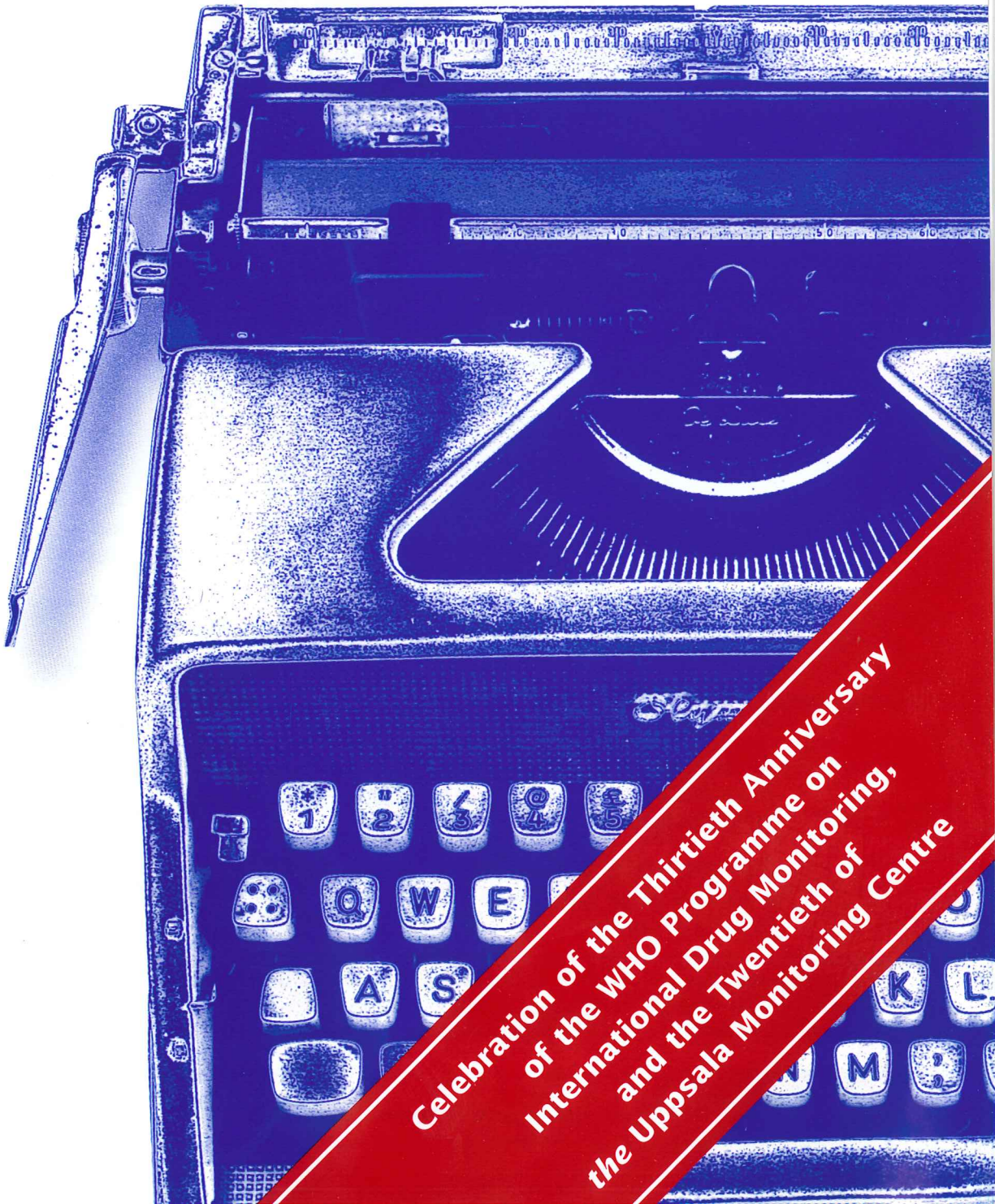
Uppsala reports

For everyone concerned with the issues of pharmacovigilance and toxicovigilance

- WHO Drug Programme News
- New Centre in Italy
- News from Around the World
- UMC changes with the times



Celebration of the Thirtieth Anniversary of the WHO Programme on International Drug Monitoring, and the Twentieth of *the* Uppsala Monitoring Centre

MESSAGE FROM RALPH EDWARDS, DIRECTOR

Celebration of the thirtieth anniversary of the WHO Programme on International Drug Monitoring, and the twentieth of *the* Uppsala Monitoring Centre

We have come a long way since 1968! Thirty years of international drug monitoring have seen great progress and changes and many new challenges. It's become clear that the evaluation of collected case material through spontaneous reporting is the most important way of signalling new concerns about drugs. Now, there are 50 countries worldwide actively involved in the enterprise.

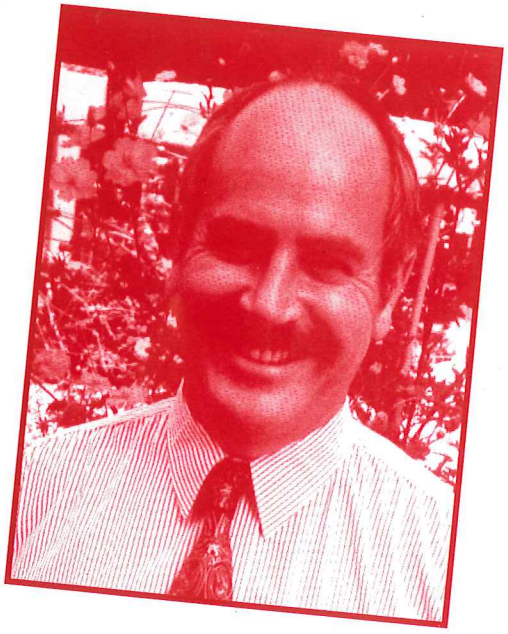
The international partners in the work have expanded. The pharmaceutical industry, consumers and academics have all become more involved in the signal generating process. They are involved in further evaluation of signals in the laboratory and from the epidemiological perspective. Communication of information to the health professions and public has become an increasing priority.

The scope of the work now includes:

- traditional herbal medicine safety
- the toxicology of drugs, and
- viewing drug safety as a continuum from development to obsolescence.

A major philosophical development has been to see drug safety much more clearly and scientifically as a benefit-to-risk balance, even comparing between drugs. In the past there has been a tendency to consider single risk situations, deciding on their acceptability or otherwise.

Later this year we plan to have another international meeting to complement those which celebrated previous anniversaries of the WHO Programme and of the Centre in Sweden. Invitations will be sent soon, together with a programme for the meeting. The programme will be aimed at learning from the past and projecting into the next millennium where we should be going in drug safety.



We look forward to sharing with you the challenges, and developments in drug safety both in the coming year and into the future.

Our thanks and appreciation to all of you who have worked with us over these many years in this important work.

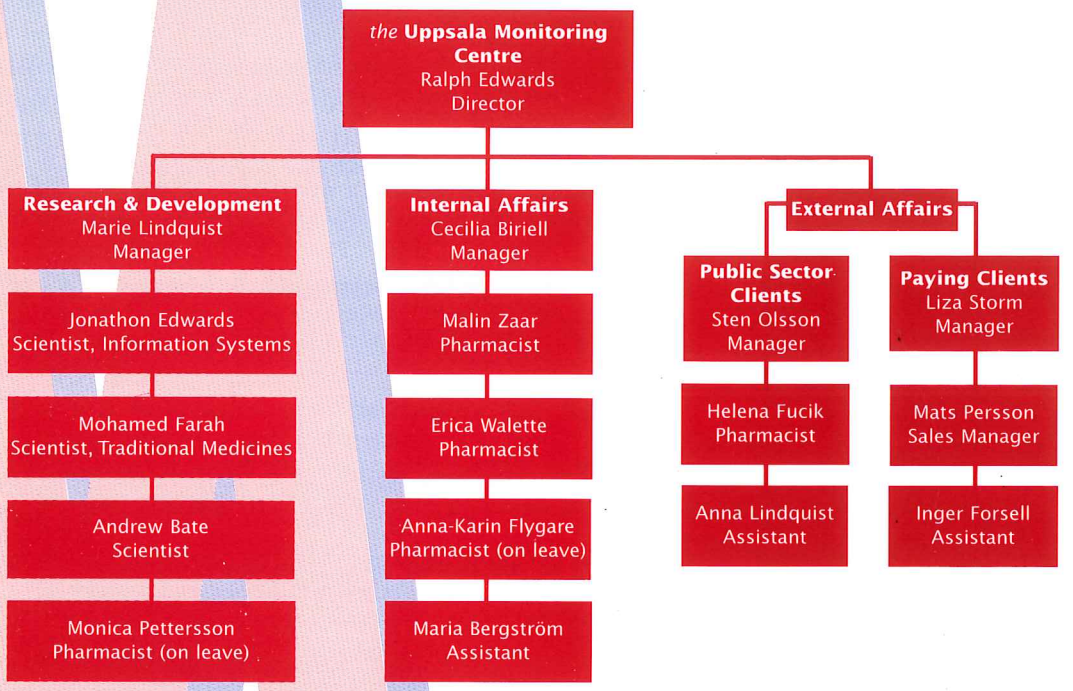
I. Ralph Edwards

UMC CHANGES WITH THE TIMES

Not only did we change our name in 1997 and move to new, bigger offices, we also tackled our internal organisation to meet the new demands of a busy, growing programme. The chart shows you just what we're all up to now.

Inger Forsell

Erica Walette



The *Internal Affairs Department* is responsible for updating and maintaining the WHO adverse reaction database, (now containing more than 1.8 million adverse reaction case reports from 50 countries), and for internal management of the Centre.

The main activities of our *Research & Development Department* are presently to:

- *develop UMC services over the Internet*
- *to improve methods for monitoring of traditional medicines,* and
- *to do methodological research in ADR signal analysis, focused on using international drug utilization data and Bayesian neural network methodology.*

The External Affairs Department is divided into two sections. One concentrates on providing information, training and other services to WHO Programme members and other clients in the public sector. The other serves paying clients, mainly within the pharmaceutical industry, with pharmacovigilance tools like the WHO Drug Dictionary and the WHO Adverse Reaction Terminology (WHOART).

In early 1998 there were two new arrivals. Inger Forsell is our new sales assistant who will also take care of accounting for the Centre. Erica Walette, replacing Monica Pettersson during her extended maternity leave, will mainly be working on the processing of incoming adverse reaction reports.

Favourable Offer for ADR Software

One of our duties is to support the development of national systems for collection of drug safety information. The lack of adequate off-the shelf computer software at affordable prices to support the work of pharmacovigilance centres, has been a major obstacle to the establishment and development of such centres in countries with limited resources. To remedy the situation we have, in a joint project with our computer service company PharmaSoft, developed a software with all functions needed to support a small or middle sized national drug monitoring centre. The computer programme also allows convenient reporting to the WHO database. This software, called PS Drug Watch, is now offered to national pharmacovigilance centres in a one-PC-version at the favourable price of US$1500.

In connection with this offer, PharmaSoft is also presenting a stand-alone version of their comprehensive product information system, developed to support all activities involved in the drug registration process, for drug regulatory authorities. This product, PS Regulator Light, is offered at the same favourable price of US$1500.

Further information about the products from Sten Olsson at UMC or Sven G.Johansson at PharmaSoft phone +46-18-185 400 or fax +46-18-109 200

Courses & Meetings in PHARMACOVIGILANCE

COURSES

■ **Instituto de Saud Publica de Chile** is going to organize a training course in adverse reaction monitoring in Santiago de Chile, 15 - 20 June, 1998. The syllabus is based on that developed by UMC for the two-week training course run in Uppsala 1993-96.

For more information please contact:

Dr Q. F. Cecilia Morgado-Cadiz
Centro Nacional de Informatión
de Medicamentyos y Farmacovigilancia,
tel +56-2-239 9769,
fax +56-2-239 8760 or
e-mail: cmorgado@ispch.cl

■ **The pharmacovigilance department of ANMAT** the Argentinian Adminsitration for Control of Drugs, Food and Medical Devices, is setting up a pharmacovigilance training course in 9 modules to run from April to November 1998.

For more information please contact:

Dr Mabel Foppiano or Ms Viviana Bollogna,
tel/fax +54-1-340 0866 or
e-mail: snfvg@anmat.gov.ar

■ At *the* **UMC** we have decided again to organize an international training course in adverse reactions and adverse reaction monitoring in Uppsala. It will be held the first two weeks of December 1998 and will be combined with an anniversary symposium to celebrate 30 years of the WHO Programme and 20 years of *the* Uppsala Monitoring Centre. Invitations will be widely distributed to our contacts throughout the world.

The contact person at *the* UMC is **Sten Olsson.**

The 21st Annual Meeting of National Centres Participating in the WHO Programme for International Drug Monitoring (1998)

This meeting will be organized by The Ministry of Health, Japan 8-11 September 1998

Invitations are expected to be distributed soon from WHO headquarters, Geneva

MEETINGS

■ **Management Forum** is organizing its 10th Annual Conference on Pharmacovigilance in London 9 - 10 March, 1998. The title is 'ADR Monitoring Across Europe and USA'.

Information will be provided by
phone +44-1483 570099, fax +44-1483 536424 or
e-mail: management_forum@psilink.co.uk

■ A round table conference with the theme 'Impact of Pharmacovigilance. Old Problems and New Challenges'. will be organized 16 - 17 March, 1998 in Costa Rica.

For more **Information** please contact Dr Albin Chaves Matamoros, phone +506-222 1878, fax +506-257 7004 or e-mail: farmaco@info.ccss.sa.cr

■ **A CODATA/ESOP** - conference with the theme 'Pharmacovigilance: Information Highway Tools for Adverse Reactions - Implications on Drug Design and Pharmacogenetics' will be held in Chambéry, France 20 - 21April, 1998.

Information from Prof. René-Jean Royer,
phone +33-3-835 92617, fax +33-3-835 92621 or
e-mail: pharmaco@pharmaco-med.u-nancy.fr

■ **IBC UK Conferences Ltd** will organize a meeting on 'Regulatory Requirements for ADRs and Adverse Events' in London, 20 - 21 April, 1998.
Information by phone +44-171-637 4383
fax +44-171-631 3214 or e-mail:caroline.elliott@ibcuk.co.uk

■ On 4 - 5 June 1998, **Smi** will organize a conference in London with the title, 'Successfully Meeting Global ADR Requirements'.

Information from Jane Falconer,
phone + 44-171-827 6072, fax +44-171-827 6073 or
e-mail:100531.3067@compuserve.com

■ **The International Society for Pharmacoepidemiology (ISPE)**, will organize the 14th International Conference on Pharmacoepidemiology at Hotel Inter-Continental, Berlin, Germany on 16-19 August, 1998.

For **information** contact Katrina Crist,
phone + 1-202-416 1641, fax: + 1-202-833 3843 or
e-mail: kcrist@slackinc.com.
The abstract deadline is February 28, 1998.

■ **The European Society of Pharmacovigilance (ESOP)** will have its sixth annual meeting in Budapest, Hungary, 28 - 29 September, 1998.

Further **information** may be received from
János Borvendég or Sándor Elek, The National ADR Monitoring Centre, phone/fax +36-1-215 8977

■ **The national ADR monitoring centre in Malaysia** is organizing a national conference with invited guests from the ASEAN region the first week of November, 1998.
For more **information** please contact Ms Abida Haq,
phone + 60-3-7573611, fax +60-3-7562924 or
e-mail: ah@bpfk.gov.my

Monitoring of herbal medicines: Your support is needed!

by **Mohamed Farah**, Scientist (Traditional Medicines) *the* UMC

Plants have been the primary source of food and medicine for people of every culture throughout the world. However, practitioners of traditional medicine need to be more aware of the problems of toxicity. They must learn that infrequent adverse drug reactions will not be recognized without the existence of a formal system of reporting negative experience. Dangers of dual treatment, mixing traditional and orthodox treatments, should be recognized by both traditional and modern health practitioners. Physicians who have patients taking any particular medicinal plant should try to document negative experiences, in order to gather enough scientific information about the adverse effects of the herb. Because adverse drug reaction reports are a critical source of herbal drug safety information, *the* Uppsala Monitoring Centre is seeking your help in detecting and reporting any herbal adverse reactions. Your continued support is crucial in building a more complete herbal drug safety profile. *the* UMC is grateful to all who are reporting suspected herbal adverse reactions to a national centre.

TAXONOMIC BOTANY

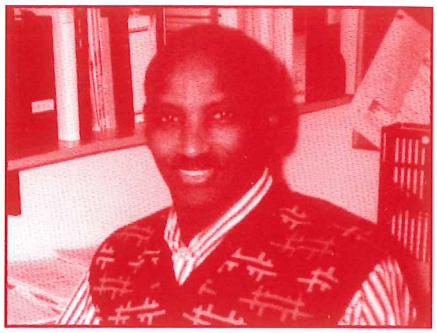
The renewed interest in the western world in plants used in traditional medicine, and the rapidly growing interest in developing countries to start research programs in this area have, unfortunately, not emphasized the great importance of taxonomic botany and documentation for such research. There is a need to adopt the most commonly used binomial names (including their binomial synonyms) for medicinal plants, to eliminate the confusion created by the common names.

Artemisia absinthium L. for example, contains an active narcotic derivative, which can cause central nervous system disorders and generalized mental deterioration. This herb has at least eleven different common names (wormwood, absinthium, absinth, absinthe, madderwort, wermuth, mugwort, mingwort, warmot, magenkraut and herba absinthii), seven of which bear no resemblance to the botanical name. Because only common names are used, Heliotropiumeuropaeum (heliotrope), containing pyrrolidine alkaloids, potent hepatoxins, is often confused with Valerian officinalis (garden heliotrope), containing valepotriates, which act as a sedative and muscle relaxant in laboratory animals.

Often there is uncertainty about the identity of plants reported to cause an adverse reaction. The exact scientific name of the plant, the plant part used and the name of the manufacturer are very important pieces of information when writing ADR reports on medicines. Solving the existing problems requires the collaboration of botanists, phytochemists and pharmacologists.

SEEKING GLOBAL STANDARDS

the Uppsala Monitoring Centre has established a project with the aim



Mohamed H. Farah

of attaining global standardization for herbal medicines. The scope is to standardize information about herbal medicines, including their scientific names and therapeutic implications, which can vary widely between countries. The structure of the ATC-system, developed for classification of orthodox medicines, is employed in this work. *the* UMC group is collaborating with the University of Exeter and the Royal Botanical Gardens at Kew in the UK, and with several other international experts.

In the WHO database there are presently 8985 case reports including a herbal preparation suspected of causing the adverse reaction. The most commonly reported reactions are:

Diarrhoea	121
Tachycardia	62
Anaphylactoid reaction	59
Hepatitis	57
Bronchospasm	49
Convulsion	39
Hallucination	39
Hypertension	39
Circulatory failure	37
Thrombocytopenia	36
Respiratory depression	33

We need more reports - and more accurate information!

NEW REFERENCE CENTRE CONNECTED TO THE WHO PROGRAMME

In November 1997 the Institute of Pharmacology of the University of Verona, Italy, headed by Professor Giampaolo Velo, was designated as a Reference Centre for Education and Communication within the WHO Programme for International Drug Monitoring, by WHO headquarters, Geneva. The department has in the past made important contributions to the development of communications in pharmacovigilance as an major topic within the Programme. Professor Velo was instrumental in organizing the meetings leading to the 'Verona-initiative' and the 'Erice Declaration'. Recognition of this contribution by WHO facilitates further initiatives in this area. A first meeting of the Education and Communications Group will soon take place.

Understanding Each Other

International Work on Effective Communications

Enclosed with this edition of *Uppsala Reports* you'll find a copy of The Erice Declaration. This was one of the results of the International Conference on Effective Communications in Pharmacovigilance held in Erice, Sicily in September last year.

The meeting was attended by over seventy people from thirty countries from every continent and hemisphere. Their commitment was to explore the complex issues of drug safety and benefit-risk communication, and of the ideal of rational prescribing.

Their useful work in examining the issues will be published later this year as a monograph which will be available from the Uppsala Monitoring Centre. Watch out for further information!

Dramatic expansion of the WHO Drug Monitoring Programme

In the previous issue of Uppsala Reports we described the new national centre in Russia and new contacts established in India. Since then Russia has submitted adverse reaction case reports to UMC and become an official member of the WHO Programme. At almost the same time the Peoples' Republic of China submitted the first batch of reports and applied for membership in the Programme. India recently did the same, now nominating a national centre. Applications for membership were recently also received from Armenia and Macedonia although ADR reports have not yet been received from these countries.

The implications of these new countries entering the WHO Drug Monitoring Programme are considerable. Information will be received from drug markets that are different from those now mainly represented in the WHO database, with different population genetics, healthcare system and therapeutic traditions adding to the value of the diversity of the WHO collection of information. It will also mean that the WHO Drug Dictionary will be enriched with drug names used in these countries only. The WHO database and information shared within the WHO drug safety network will be accessible to decision makers responsible for public health for another 2.2 billion people.

Contact information to the new national centres:

ARMENIA

Dr Samvel Azatyan

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15, Moskowian Street
Yerevan 375001

phone: +374-4-528 615
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e-mail: chinaadr@public.bta.net.cn

CIOMS Group Takes the Work Forward

Building on the work begun in Erice, a CIOMS working group met in Dublin in December with the aim of providing best practice guidelines for all communications in the field of pharmacovigilance. Their work will continue for the next six to eight months, prior to conclusions being published as a CIOMS monograph.

OBITUARIES

PROFESSOR EMERITUS GARTH MCQUEEN died in his home in Dunedin, New Zealand in June, 1997. Garth was a great man, having scholarship, vision and integrity. He and a few others with international vision started the work in drug and chemical safety that has helped to make the world a safer place. The linking of drugs with chemical safety in general and service and research functions has become the recommended approach of the WHO, and New Zealand was the pioneer of this approach. Prof. Garth McQueen was one of the first clinical toxicologists, using his general medical and clinical pharmacological knowledge to great effect. He was a person with a profound interest in his work, and initiated what was to become the National Toxicology Group in New Zealand. The Intensive Medicines Monitoring Programme is another unique development that started through his work, and is still admired worldwide.

Both other specialists and students held Garth in great regard for his clinical knowledge and wisdom. He was a good teacher and the sometimes stern exterior was frequently enlivened by original humour. But he did not suffer fools gladly, and was not afraid to stand against the flow for what he thought was right.

He was very active in WHO circles. New Zealand was one of the original countries involved in the WHO Programme for International Drug Monitoring.

The fact that he learned to ski when he was about 60 perhaps gives some impression of the determined person he was!

DR FRANZ ROSA, who served as an epidemiologist and teratologist for the FDA in United States 1979 - 1996 died from cancer on 3 October, 1997. Dr Rosa was for many years an active and much valued signal reviewer in the teratology area for the WHO Drug Monitoring Programme. A Franz Rosa Scholarship Fund has been established by the Organization of Teratology Information Services in the US.

RECENT PUBLICATIONS FROM *the* UMC

1. **I. Ralph Edwards**
   Who cares about pharmacovigilance?
   European Journal of Clinical Pharmacology (1997) 53:83-88
2. **M.M.S. Stahl, M. Lindquist, M. Pettersson, I.R. Edwards, J.H. Sanderson, N.F.A. Taylor, A.P. Fletcher, J.S. Schou**
   Withdrawal reactions with selective serotonin re-uptake inhibitors as reported to the WHO system.
   European Journal of Clinical Pharmacology (1997) 53:163-169
3. **R.H.B. Meyboom, A.C.G. Egberts, I.R.Edwards, Y.A. Hekster, F.H.P. de Koning, W.J. Gribnau**
   Principles of Signal Detection in Pharmacovigilance.
   Drug Safety (1997) 16:355-365
4. **I.R. Edwards, B. Hugman**
   The Challenge of Effectively Communicating Risk-Benefit Information. Drug Safety (1997) 17:216-227
5. **R.H.B. Meyboom, Y.A. Hekster, A.C.G. Egberts, F.W.J. Gribnau, I.R. Edwards**
   Causal or Casual? The Role of Causality Assessment in Pharmacovigilance. Drug Safety (1997) 17:374-389
6. **A. Bate, M. Lindquist, I.R. Edwards, S. Olsson, R. Orre, A. Lansner, R.M. de Freitas**
   A Bayesian neural network method for adverse drug reaction signal generation.
   European Journal of Clinical Pharmacology (in press)
7. **S. Olsson**
   Role of WHO Programme on International Drug Monitoring in Co-ordinating Worldwide Drug Safety Efforts. Drug Safety (in press)

PRODUCT NEWS

Computerized WHO Adverse Reaction Terminology (WHOART) and WHO Drug Dictionary

New updated versions containing information up to and including the fourth quarter 1997 will be available at the end February/beginning of March.

The English version of ***WHOART***, December 31, 1997, will be available in hard copy in March/April. ***ART Access***, the computerized ART with search facilities, will be updated to include information as per the fourth quarter 1997. It will be available during March.

The hard copy version of ***WHO Drug Dictionary*** March 31, 1998, as well as the ***DD Access***, standard version, will be available in June.

The Centre will attend the following meetings during the next few months and exhibit its products:

March 30 - April 1:
DIA 10th Annual EuroMeeting, Nice, France

April 22 - 24:
ACRP's 22nd Annual Meeting, Anaheim (CA), USA

May 13 - 15:
IIR's Adverse Drug Reaction Conference, Orlando (FL), USA

June 7 - 11:
DIA 34th Annual Meeting, Boston, USA

On **May 18 - 20** UMC will hold its annual planning conference which means that availability of staff members will be very limited.

News from Around the World

AUSTRALIA

The former head of the national pharmacovigilance centre in Australia, **Dr Alain Rohan**, has now become director of pharmacovigilance at the company 3M in Saint Paul, Minnesota, USA.

He may be contacted by fax (+1-612-733 6068) or e-mail (arohan1@mmm.com)

EUROPEAN UNION

At the office of the Commission of the European Union in Brussels, Directorate **Dr Ana de Vasconcelos Batalha** now has the responsibility for pharmacovigilance issues. She succeeds Mr Philippe Meyer, who has moved to DG I. Dr Batalha paid a very short visit to Uppsala in November' 97.

NEW ZEALAND

The Centre for Adverse Reactions Monitoring (CARM) has a new head after Dr Peter Pillans took up a position as Professor of Clinical Pharmacology at Princess Alexandra Hospital, Brisbane, Australia in late 1997. He is replaced by **Dr David Coulter**, the previously long-serving head of the Intensive Medicines Monitoring Programme.

SOUTH AFRICA

Dr Ushma Mehta supervised a pharmacovigilance training course held in Cape Town on 29 November. There were 14 participants including representatives from Ethiopia, Sudan, Scotland, Mozambique, Ghana and South Africa. The principles of problem-based teaching were used. Questions like when to report, who should report, confidentiality and the special concerns of African countries, created a lot of discussion during this short course that may be repeated next year.

SUDAN

Commissioned by the WHO Regional Office for the Eastern Mediterranean, **Dr Ronnie Meyboom** of the Netherlands spent the first two weeks of 1998 in Sudan, lecturing about pharmacovigilance and how to set up a national centre. His report will contain a plan on how such a centre may be established in the country.

TANZANIA

Ms Rose Shija, the former head of the Tanzania Drug and Toxicology Information Service (TADATIS) in Dar-es-Salaam, has left the centre for another post in the Ministry of Health. **Mr Henry Irunde** is now head of the centre which has established new headquarters within the premises of the Pharmacy Board.

The relevant address is TADATIS, Pharmacy Board, P.O.Box 77150, Dar es Salaam, Tanzania

Pharmacovigilance development in Portugal

The national pharmacovigilance centre, under the direction of Dr António Faria Vaz, recently investigated the state of pharmacovigilance in Portugal by:

- interviewing former staff members
- interviewing opinion leaders in the pharmaceutical industry, members of the medical and pharmaceutical professions and their respective associations
- analysing standard operating procedures in pharmacovigilance
- evaluating available adverse reaction data

The following main obstacles to development of pharmacovigilance in the country were identified:

- lack of technical and scientific resources
- lack of information about the reporting system
- excessive centralization
- lack of reporting culture
- lack of research in the area

An action plan to be carried out 1997-99 has been developed. The following elements are included

1. Creation of local reference centres located in universities and/or teaching hospitals
2. Dissemination of information about the national pharmacovigilance system to all health authorities and hospital boards. Meetings with directors of hospitals and clinics will be organized in all parts of the country
3. Creation of a pharmacovigilance bulletin to be sent to all doctors and pharmacists four times a year
4. A national campaign to promote adverse reaction reporting will be launched through specialized media, organized by a marketing company
5. Training courses on adverse drug reactions for hospital doctors and GPs will take place in collaboration with university pharmacology departments and the local reference centres
6. Establishment of a research promotion fund

For further information about the project, please contact
Dr António Faria Vaz
phone + 351- 1-7908558,
fax + 351- 1-7959116 or e-mail: infarmed@mail.telepac.pt

Your Communications Materials Wanted!

the Uppsala Monitoring Centre has already published a first reference collection* of communications materials produced by member countries. The aim is to make available good ideas from round the world which can be adopted and adapted by anyone.

The folder includes pictures of actual posters, bulletins, video and audio tapes, calendars, media packs and jotter pads - and much more! - which imaginative professionals round the world have developed to promote the cause of drug safety, ADR awareness and so on.

the UMC is keen to extend the content of this collection with examples of materials from many more countries: please do send yours in to Sten Olsson!

*Available on request at no charge to member countries or for US$100 to non-members and other customers.

Contact Liza Storm in Uppsala if you'd like a copy.

the Uppsala Team

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Research and Development Manager: Marie Lindquist
Sales and Promotions Manager: Mats Persson
Scientist, Traditional Medicines: Mohamed H. Farah
Pharmacists: Helena Fucik, Monica Pettersson, Malin Zaar, Erica Walette, Anna-Karin Flygare
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