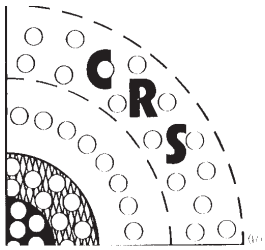
UKCRS Newsletter



United Kingdom Controlled Release Society http://www.pharmweb.net/ukcrs.html
Editors: Tony D'Emanuele & Anya Hillery No.3 August 1997

Welcome to the Third UK Controlled Release Society Newsletter. The UKCRS is entering its fourth year and has grown from strength to strength, evident by the great success of the January Symposium in Manchester. The UKCRS Committee has had a transformation with Prof. Clive Wilson as the new chairman and several new committee members. If you would like to hear the latest news about the UKCRS why not join our Internet mailing list, information of which is in this Newsletter (UKCRS on the Internet).

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A Message from the New Chairman

UKCRS is now entering the fourth year as a local chapter with three successful annual meetings completed and much more activity planned for 1997 and 1998. Our previous chairperson, Professor Ruth Duncan aided by Professor Martyn Davies as secretary, have stepped down this year leaving myself and Marianne to carry on the good work aided and abetted by our expanding committee. Ruth and Martyn did a sterling job in getting the chapter started and we will always be in their debt. We are still fortunate that through Ruth, Duncan Craig and Professor Florence we are able to hold our planning meetings at the Square, so you can see the comment about debt is strangely accurate.

This autumn we will hold a joint meeting with the British Pharmaceutical Society at Scarborough on Tuesday 17th September. The title of the symposium is : "New Approaches to Drug delivery : from design to market : key issues in pre-clinical drug delivery ". There probably are even more colons in the presentations than in the title as I get to present my fun images of the gastrointestinal tract. Professor Barry Hirst will talk about CaCo-2 cell lines and Professor Richard Guy will tell us about the latest developments in iontophoresis. Dr Jane Lawrence of King's will chair the symposium and we will have more than 40 poster presentations. Come along and enjoy the event.

Next January we will host our 4th meeting and the committee are busy trying to get the programme finalised. We have a number of joint presentations planned for 1998 and other members of the committee are liasing with their counterparts to organise the events. My thanks to all of the new members for remaining enthusiastic and committing time so that we can maintain the impetus.

We are seeking to expand our boundaries by joining with Ireland to make a larger local chapter. The link through David Brayden (Elan Corporation) in Dublin should provide convivial and informed support. Some of you who went to the Dublin meeting on peptides in 1995 will remember what a good time you had. Failing that, have a look at the Journal of Controlled Release May 1997 to remind yourselves what you missed. Finally, we were the first pharmaceutical organisation to develop a web site (thanks to Dr Tony D'Emanuele our enthusiast at Manchester) and we look forward to remaining a dynamic, innovative group embracing all aspects of controlled release.

Clive Wilson, Chairperson of UKCRS

The UKCRS Committee

The UKCRS Committee has changed dramatically in recent months with several new faces joining. A short biography is presented of the current members.

Saghir Akhtar - Organiser 1998 Meeting

Address: Department of Pharmaceutical and Biological Sciences, Aston University, Aston Triangle, Birmingham B4 7ET

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Saghir Akhtar is Reader in Pharmaceutical Sciences at The University of Aston. He received his PhD in polymeric drug delivery systems from the University of Bath in 1990 and did his post-doc. at the University of North Carolina School of Medicine at Chapel Hill where he studied the cellular uptake mechanisms of antisense oligonucleotides. In 1991, Saghir moved to The Department of Pharmaceutical and Biological Sciences at Aston University. His current research interests include the cellular delivery and biological evaluation of antisense oligonucleotides and ribozymes as novel therapeutic agents for anticancer and antiviral applications.

Marianne Ashford - Secretary

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Marianne is currently working in the Pharmaceutical Research Group of Zeneca Pharmaceuticals. After, completing a PhD at the University of Manchester on oral drug delivery to the colon, Marianne joined Zeneca. She still maintains an interest in oral controlled release delivery systems. Marianne's current position is leading a team which is responsible for providing the biopharmaceutical support to drug discovery projects.

Anne Brindley - Programme Organiser 1998 Meeting

Address: Astra Charnwood, Bakewell Road, Loughborough LE11 5RH
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Anne is a Team Leader at Astra Charnwood. After graduating from the University of Bath with a degree in Pharmacy, Anne worked for Glaxo Group Research, on the formulation of solid dosage forms. Anne then left Glaxo to undertake a PhD at the University of Nottingham on the site-specific delivery of polymer colloids. After completing her PhD, Anne returned to Glaxo at Ware, working on the development of dry powder inhalers and then metered dose inhalers. Anne joined Astra Charnwood in 1996 where she currently works on metered dose inhalers.

Alan Coombes - Industrial Liaison

Address: Quadrant Healthcare, Maris Lane, Trumpington, Cambridge CB2 2SY
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Alan studied material science at the University of Nottingham and received a PhD in polymer physics from the University of Bristol. Research in bioengineering at University College London was followed by two years at the University of Texas working on biodegradable polymer implants for bone repair. In 1990 he took up a position as a research fellow in the Department of Pharmaceutical Sciences at the University of Nottingham working on microparticulate systems for drug delivery, vaccine development and controlled release of proteins and peptides. Recently he took up a position with Quadrant Healthcare working in the area of protein and peptide delivery.

Duncan Craig - Academic Liaison

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Duncan is a senior lecturer in the School of Pharmacy at the University of London. After graduating from Bath University, Duncan undertook a PhD on dielectric spectroscopy of pharmaceuticals. His current research interests embrace the assessment of physical structure of materials and more recently, biological materials using biophysical techniques.

Tony D'Emanuele - External Relations

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Tony is a lecturer in the Department of Pharmacy at the University of Manchester. After graduating from The School of Pharmacy, University of London, Tony undertook a PhD at the University of Bath on responsive electrophoretic drug delivery. Tony took up his current appointment after an eighteen month postdoctoral fellowship at the Massachusetts Institute of Technology where he investigated the use of ultrasound to modulate drug release from biodegradable implants. Tony is currently researching pulsatile and responsive delivery systems, biodegradable polymeric systems, and the delivery of genes into cells by means of sonication.

Anya Hillery - External Relations

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Anya is a lecturer in Pharmaceutical Sciences at the Department of Pharmacy, University of Brighton. After graduating from Trinity College Dublin, Ireland, she carried out her PhD at the School of Pharmacy, Brunswick Square, University of London, on novel particulate delivery systems for the oral absorption of peptides. She continued this research as a Maplethorpe Research Fellow at the Square. Her current research interests include micro- and nano-particulate drug delivery systems, oral drug delivery and oral immunization.

Hiep Huatan - Organiser 1998 Meeting

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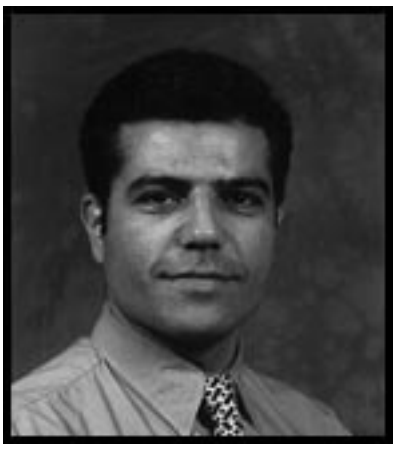
Hiep is a Research Scientist in the Exploratory Drug Delivery Group, Pfizer Central Research. After graduating from the University of Nottingham, Hiep undertook a PhD at the University of Manchester on the characterisation of multicomponent polymeric drug delivery systems; an area of research which he maintains an active interest. In his current position, Hiep is involved in the provision of biopharmaceutics support for a number of human medicinal and animal health discovery projects. More recently, Hiep has also been involved in product enhancement initiatives at Pfizer.

Ali R. Rajabi-Siahboomi - Academic Liaison



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Ali is a lecturer in the School of Pharmacy and Chemistry, Liverpool John Moores University. After graduating in Pharmacy from Nottingham University, Ali undertook a PhD at Nottingham University on HPMC in hydrophilic matrix dosage forms. Ali's current research interests include: formulation and characterisation of oral controlled release matrices and lymphatic drug delivery.

Peter Scholes - Programme Organiser 1998 Meeting

Address: 3M Healthcare Ltd., Conventional Drug Delivery, Morley Street, Loughborough, Leicestershire LE11 1EP

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Peter is currently working within the Conventional Drug Delivery Department at 3M Healthcare in Loughborough. After graduating in Pharmacy from the Department of Pharmaceutical Sciences at the University of Nottingham, Peter returned there to complete a PhD on the development of a biodegradable microsphere carrier system for site specific drug delivery. His current position at 3M is as the liquids and creams development section leader with responsibilities for both new product development and also the provision of technical support to existing marketed products.

Mike Tobyn - Continuing Education

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Mike is a lecturer in pharmaceutical technology in the School of Pharmacy and Pharmacology at the University of Bath. He is a Pharmacist who graduated from the Strathclyde University. He also did his PhD, on formulation issues related to mucoadhesive drug delivery devices, at Strathclyde. He has been at Bath since 1994. Here he does research on oral controlled release systems, drug delivery to the lung and the study and development of excipient particles.

Clive Wilson - Chairperson

Address: Department of Pharmaceutical Sciences, Royal College, University of Strathclyde, 204 George Street, Glasgow G1 1XW

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Clive is the current J P Todd Professor of Pharmaceutics at Strathclyde having taken up the post from Professor Sandy Florence in 1992. He admits an origin from strange backgrounds (physiology, biochemistry, parisitology) which probably does not account for his interest in pharmaceutical sciences. During his years at Nottingham Medical School, he helped develop scintigraphic techniques used in formulation evaluation in man. In Scotland, he has continued his interest in ophthalmic and gastrointestinal drug delivery and in newer methods of non-invasive drug monitoring.

Jane Worlock - Treasurer

Address: JAGO Pharma AG, Maison La Serre, 31230 Anan, France

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Jane recently joined the international operations department of JAGO Pharma AG to work on European business development from her base in South West France. JAGO specilaises in oral drug delivery with it's Geomatrix® and inhalation technologies, and is a subsidiary of Skye Pharma plc (located in London).

Report on the 3rd Annual UKCRS Symposium - Manchester

The Third United Kingdom Controlled Release Society symposium on 'Controlled Drug Delivery: Current Perspectives and Future Trends' took place at the University of Manchester on the 6th of January 1997. The successful event was organised by Dr Antony D'Emanuele (University of Manchester) and was the first ever pharmacy related symposium to be broadcast live around the world via the Internet. Despite the adverse weather conditions, over 100 participants from the United Kingdom, North America and Europe were present at the meeting. The morning session was chaired by Professor Malcolm Rowland (University of Manchester) and Dr Marianne Ashford (Zeneca Pharmaceuticals, UK). Professor Rowland welcomed the attendees to the University of Manchester. He spoke of Manchester's long history of contribution to scientific progress. Professor Nicholas Peppas (Purdue University, USA), chairperson of the CRS Global Chapters Committee, officially opened the symposium with a message from the Controlled Release Society. Professor Peppas said that Professor Tsuneji Nagai (Hoshi University, Japan), president of the CRS, was delighted at the success of the UKCRS and their annual symposia. He gave a brief overview on the origin of the CRS and spoke of its continual growth and internationalisation. The Society now has members in over 85 countries. Professor Peppas was pleased to announce the recent establishment of local sections of the CRS in many countries around the world. He ended his opening speech by promoting the forthcoming CRS symposia and meetings in Buenos Aires, Athens, Tenerife, Italy, India and Stockholm.

The speakers at the Manchester Meeting. From left to right: Prof. David Clarke, Prof. Martyn Davies, Prof. Nicholas Peppas, Dr. Stephen Zale, Dr. A. D'Emanuele and Dr Anthony Phillips.

Professor David Clarke (University of Manchester) was the first speaker of the day and gave an informative talk about his research into bioresponsive lipid based delivery systems. Professor Clarke described the limitations of current biosensing technology and said that few biosensor devices are

considered reliable enough to be used *in vivo* as monitoring devices, or for feedback control. He emphasised that more intimate coupling of biosensors with release functions was required before useful, bioresponsive release systems could be developed. In nature, biomembranes are used to couple biorecognition events to a variety of effector functions. Professor Clarke explained that by integrating the biorecognition events used in biology and *in vitro* diagnostics into lipid bilayers, targeted molecular biosensors for screening and bioresponsive controlled release systems could be developed. He also discussed the use of biomimetic peptides to produce quantitative, bioresponsive release and transport of small molecules and proteins across lipid bilayers, and to bind reversibly to the variable and non-variable regions of immunoglobulins.

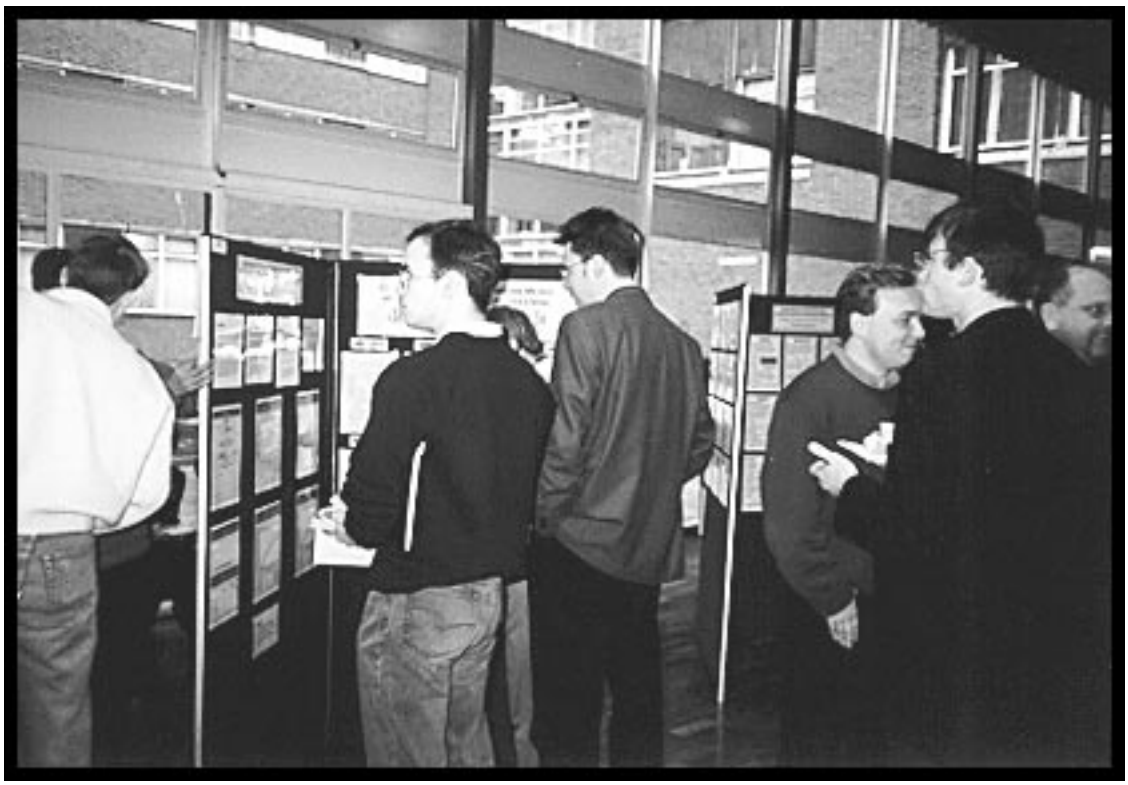
"Understanding Surface Macromolecular Interactions in the Design of Therapeutic Systems" was the title of Professor Martyn Davies' talk. Professor Davies (University of Nottingham) explained the importance of surface interactions in understanding the performance of advanced drug delivery systems at the molecular level. A number of advanced biophysical techniques have been developed to define surface phenomena. Professor Davies described two of these techniques, Atomic Force Microscopy (AFM) and Surface Plasmon Resonance (SPR), which he has used in his work. He explained that AFM was a relatively inexpensive technique and works in a similar way to a record player, in that it uses a very sharp tip to probe surfaces. AFM produces very high resolution 3-D images of molecular structures and surfaces and can provide useful data on molecular interactions. It can be used in almost any environment, requires little sample preparation, and can provide time-resolved data, therefore allowing molecular processes taking place *in situ* to be followed. AFM has been used successfully to image DNA-enzyme interactions, blood-clotting processes, release of protein-based drugs from polymeric drug delivery systems, the escape of a virus from its cellular host, the hydration of dextran molecules and phase separation in polymer blends. Professor Davies showed how the atomic force microscope could be adapted for measuring forces of dissociation between macromolecules e.g. biotin and streptavidin. He then discussed the technique of SPR and its use in investigating the adsorption of polymers to surfaces. Professor Davies ended his talk by explaining that by combining these techniques a greater insight into understanding molecular interactions could be gained.

Professor Nicholas Peppas returned to the podium to deliver his talk on the design of new biomaterials for drug delivery. Professor Peppas discussed the potential of many novel polymeric materials in a wide range of controlled drug delivery applications. He spoke about the use of novel pH or temperature-responsive grafted polymer hydrogels to achieve pulsed, "on-off" controlled peptide drug delivery. These "intelligent" hydrogels undergo dramatic swelling and collapse triggered by very small changes in the pH or temperature of its immediate environment. This swelling and collapse corresponds with increase or decrease in the mesh size of the polymer matrices, thus allowing control over the efflux of drug out of the hydrogels by manipulating the pH or temperature. Professor Peppas discussed the need to demonstrate that the swelling/collapse behaviour of the hydrogels is reproducible over several thousand cycles without polymer failure, and also to determine the biocompatibility of these novel biomaterials. Professor Peppas also expressed his interest in novel star polymers (dendrimers) and their applications to polymer therapeutics. He said that many of these star polymers have been shown to be non-toxic and that there was great potential in developing star polymers for controlled release applications. The structure of star polymers allow the expression of large numbers of functional groups in a relatively small volume. He explained that these functional groups could be used to immobilize enzymes.

Professor Ruth Duncan (University of London), explained the role of the UKCRS in acting as a focus for the study and development of controlled release technologies in the UK and also to provide a forum for the exchange of information within the field. She expressed her delight at the high attendance at the symposium and thanked Dr Antony D'Emanuele for organising the event. Professor Duncan was optimistic about the future of controlled release technology in the UK and said that this was

reflected in the high proportion of young scientists present at the meeting and also in the high standard of the posters on display. She said that although research into controlled release in the UK was primarily related to pharmaceutical applications, controlled release technologists working in other areas, such as agriculture, were encouraged to join the UKCRS and take part in its activities. Professor Duncan said that she would be stepping down from her position as the chairperson of the UKCRS and that Professor Clive Wilson (University of Strathclyde) would be taking over as the chairperson. She also said that Dr Colin Pouton (University of Bath) and Professor Martyn Davies would be standing down from the UKCRS committee. Professor Duncan commended Professor Davies for all the hard work and effort he has put into setting up and running the UKCRS.

The poster presentations took place after lunch and highlighted the many diverse areas that are currently being investigated in the field of controlled release drug delivery. Topics covered included anticancer agents, gene delivery, transdermal delivery, biodegradable polymers and novel hydrogels as drug delivery systems. A prize of £500 plus registration fee for the annual CRS conference that takes place in Stockholm this June was awarded to Sasa Dimitrijevic from the School of Pharmacy, University of London, and James Birchall from the Welsh School of Pharmacy, University of Wales, for the best poster presentations.



The poster session kept everyone busy at lunchtime.

The first talk of the afternoon was given by Dr. Stephen Zale from Alkermes Inc., Massachusetts, and was titled, 'Polymeric Microspheres for Sustained Delivery of Therapeutic Proteins.' At present, therapeutic proteins generally have to be administered by frequent injections due to their low oral bioavailability and short half-lives. Dr. Zale talked about a system called PROLEASE, an injectable, microsphere-based, sustained release delivery system for protein drugs. Trials in humans have shown that this system is capable of sustaining release for up to 3 weeks. Dr. Zale discussed the techniques and problems that occur in the processing and formulation of this system, including the issues of protein integrity and stability during storage and injection.

It has always been a policy of the UKCRS to encourage the work and research carried out by postgraduate students and young scientists. To this end, there then followed three short talks given by young scientists from academic institutions around the country. The first, confidently presented by Dr. Ijeoma Uchegbu from the School of Pharmacy, University of London, discussed the uses of niosomes in drug delivery. Niosomes are non ionic surfactant vesicles, which have been found to be useful drug carriers in previous *in vivo* studies. However, these agents were found to be taken up by the liver. Dr. Uchegbu described *in vivo* studies performed with new niosomes formed from N-palmitoyl muramic acid and loaded with doxorubicin. These studies showed that these vesicles avoided liver uptake, and instead were predominantly taken up by the spleen.

The poster prize winners, Sasa Dimitrijevic and James Birchall.

The next talk was given by Susan Berill, a final year postgraduate student at the University of Manchester. Susan's talk was concerned with biodegradable polycaprolactone copolymer blends. Polycaprolactone is a biodegradable and biocompatable polymer, however, its hydrophobicity makes it unsuitable for implantable polymer-drug systems, as this is indicative of poor drug loading and release properties. Susan discussed the incorporation of a polyoxyethelene moiety to increase the hydrophilicity of the polymer blend, and as such, gives rise to hydrolysis and enzymatic cleavage of the polymer, and allows the release of the drug.

The last of these 15 minute talks was given by Snjezana Stolnik from the University of Nottingham, and was entitled 'The Difference in Biological Properties of Poly(ethylene oxide) Coated Colloidal Carriers - Relation to their Physicochemical Properties.' Dr. Stolnik discussed how the adsorption of copolymers of polylactide-poly(ethylene oxide) onto colloidal drug carriers can reduce the problem of the colloid accumulating in the liver and spleen, whilst prolonging the circulation time in the blood. However, this effect is not obtained with polystyrene colloids. The work presently being carried out aims to assess whether the observed differences in the biological performance are related to a difference

in the adsorption behaviour of the polylactide-poly(ethylene oxide) on the surface of the colloids.

Dr Antony D'Emanuele from the University of Manchester gave the next talk on pharmaceutical information on the Internet. The Internet is a powerful information resource, which can provide pharmacists all over the world with the means to communicate with each other. Dr D'Emanuele talked about PharmWeb, a pharmaceutical and health information service, created by him, which has been accessed by over 110 different countries, and the UK servers alone receive over 300,000 page requests each month. PharmWeb presents scientists and patients with the opportunity to search for material in sites specifically tailored for pharmaceutical needs, whilst also offering other services, including PharmWeb appointments, information on forthcoming conferences and events, mailing lists and on-line discussion groups for the exchange of information between readers.

Dr Anthony Phillips from Glaxo Wellcome finished off the day with an industrial perspective of gene therapy. There are over 4,000 diseases which have been identified as gene disorders, and gene therapy offers the potential to cure or reduce the effects of many of these. Dr Phillips discussed the issues that face the development of these products, such as cell targeting, manufacture at the scale required, and demonstration of safety to the regulatory authorities. He then went on to give examples of viral and non-viral based systems and briefly discussed their manufacture and the way in which they work. Dr Phillips left us with the message that he believes that the first gene therapeutic will be on the market early in the next millenium.

Overall, the day was thoroughly enjoyable, with a balanced diversity of subject matter, invoking much discussion. For that, we should thank the members of the UKCRS, the local organiser, Tony D'Emanuele, and all those who presented such stimulating posters and talks.

Sai Kit Li and Samantha Watson

Report on the 24th International CRS Symposium in Stockholm

Stockholm, known as "Beauty on Water" , was the wonderful setting for the recent 24th International Symposium on Controlled Release of Bioactive Materials. The conference is now firmly established as the foremost in its field, and with over 550 abstracts and 1021 registered attendees, this year's was one of the biggest yet. State-of-the-art science, which encompassed every conceivable aspect of controlled release, was presented either in lecture or poster sessions; there were also additional workshops on International Drug Regulatory Standards and Gene Therapy, minisymposia on selected topics, and a vast area set aside for exhibitors.

Both plenary lectures dealt with the general theme of drug delivery and targeting for the future. The first was given by Professor H Wigzell (Karolinska Institute, Sweden), who talked specifically about regulation of the immune system and the importance of cytokines and chemokines in this process. Therapeutic vaccines for the future were described, and the increasing amount of research interest in mucosal immunization was discussed. The second plenary lecture was given by Dr D Breimer (LACDR, Leiden University, The Netherlands) who talked about the importance of integrating drug delivery and targeting with pharmaceutical R&D. He contested that currently, the approach was technology driven and placed too much emphasis on drug delivery systems *per se*, rather than choosing the most suitable delivery system for the drug in question.

With such an enormous conference, it is obviously impossible to adequately cover the proceedings within the limited space of this newletter, and the following comprises merely a brief list of contents:

podium and poster sessions on Oral Drug delivery, Transdermal and Iontophoretic Delivery, Delivery of Genes and Oligonucleotides, New Materials and Principles and Techniques for Drug Delivery, Pulmonal and Alveolar Drug Delivery, and Drug Targeting. Additional poster sessions covered Transmucosal Delivery, and Agricultural and Veterinary Applications of Controlled Release. There were also minisymposia on: Innovative Aspects of Controlled Drug Release, Delivery Strategies for Mucosal Immunization, Restenosis and Local Drug Delivery Strategies, and Drug Delivery to the Brain. The conference also held special themed sessions on Beyond Liposomes - Lipids as Components in Drug Delivery Systems, and Sustainable Agriculture - Low Use Rate Agrochemicals. An account of the Minisymposium on "Delivery Strategies for Mucosal Immunization" by Professor O Alpar can be found in this Newsletter.

Members who did not attend, but would like further information, are advised that the Abstract Proceeding Book can be purchased by writing to the CRS Administrative Headquarters. The Proceedings cost $80, plus an additional $65 for airmail delivery (otherwise it takes up to 12 weeks by boat) and it must be prepaid by either cheque or credit card. Non-members are advised that one can join CRS for $65 for 1997 and receive a free Proceedings with the membership. Alternatively, selected past annual conference proceedings and workshop notebooks will soon be available for loan (free of charge) to chapter members. Please contact UKCRS for further details.

All this wealth of science proceeded in a highly pleasant and convivial atmosphere. A most enjoyable welcome reception set the scene, followed later in the week by the CRS Banquet, which began with drinks in the magnificent Golden Hall of the Stockhom City Hall - where the Nobel Prizes are awarded. The banquet also saw the inauguration of Professor Ron Siegel as the new president of the society.

A particular highlight of the conference was the awarding of the Young Invesitgators Award to the past secretary of the UKCRS, Professor Martyn Davies. This is a highly prestigious award, with previous recipients including such leaders in the field as Joke Bouwstra, Rainer Muller, Ruth Duncan (UKCRS past-chairperson), Vincent Lee and Ron Siegel. We extend our warmest congratulations to Martyn.

Other good news from the conference was the announcement that the UKCRS was successful in its bid to host the 30th International CRS Symposium in 2003. The conference will be held in Glasgow. Hosting the conference operates on a yearly rotation basis between the USA, Asia and Europe, and a considerable amount of effort and hard work was required at the committee level to fight off the competition from other European cities for the 2003 slot. The hard work has paid off, and we are obviously delighted the conference will be coming to the UK.

Anya Hillery

Joint Meeting between the UKCRS and the RPSGB - 1997

The UKCRS are collaborating with the Pharmaceutical Sciences Group, RPSGB at this and next years British Pharmaceutical Conference. This year, we have jointly organised a symposium entitled 'New Approaches to Drug Delivery: From Design to Market' in which a panel of international experts will be speaking on issues relating to pre-clinical drug delivery, novel technologies in the clinic and registration and marketing of controlled release products. In addition, a contributed poster session will be run jointly between the two organisations. This conference marks the beginning of what we hope will be a long and friendly relationship with the Pharmaceutical Sciences Group and we would like to thank Drs Jayne Lawrence and Gary Martin from the PSG, with whom we have been working closely in the organisation of the symposium. We hope to continue our contribution to the British Pharmaceutical Conference next year in Eastbourne.

Duncan Craig

4th Annual UKCRS Symposium - London January 1998

The 4th UKCRS Meeting on "Continuous vs Discontinuous Drug Delivery - Current Perspectives and Future Horizons" will be held on Tuesday 6th January 1997 at the School of Pharmacy, University of London, Brunswick Sq. With speakers from both academia and industry participating, we can look forward to a well-rounded conference, reflecting many of the important current issues in the field of controlled release. The final programme plus latest news on the meeting will be circulated shortly and will also be available on the UKCRS Web page.

There will be an invited poster session at the 1998 January Meeting in London. In keeping with previous years, and further demonstrating the commitment of the CRS to support young scientists, a number of awards of £500 each will be made to the best posters. These awards will enable the winners to travel to the Las Vegas CRS meeting, June 1998.

Issues in Controlled Release

Issues in Controlled Release will focus on a particular aspect of controlled release, usually in the form of a meeting report. Colin Pouton wrote an article on gene therapy in the last Newsletter, and in this edition Professor Oya Alpar talks about vaccines. The editors are happy to consider articles/reports of meetings (~2,000 words) which can be included in this series.

Issues in Controlled Release - Vaccines: Mucosal Immunisation

Vaccines have traditionally been used as weapons against health threats. Smallpox has now been eradicated from the earth, and the polio virus is well on its way to becoming extinct. In 1993, a report of the World Bank concluded unambiguously that vaccination is the most cost-effective public health measure available. In spite of this apparent truism, vaccination has not been an overwhelming success for many reasons. The dramatic increase in patients suffering from human deficiency virus (HIV) since the early 1980s, and the re-emergence of antibiotic resistant strains of tuberculosis serve as powerful reminders that infectious diseases are an ever-present threat to the human race. There is thus a pressing need to develop ever more effective vaccines as demonstrated by the heightened interest in vaccine development.

There is also a need to explore alternative ways of enhancing the immune response, including the development of better adjuvants and to increase our understanding of vaccine immunology, especially mucosal immunity. Historically, immunisation has relied on the induction of humoral immunity by parenteral administration of vaccines. Antibodies induced in this manner, however, do not necessarily reach mucosal surfaces where most infectious agents enter the host. Mucosal immunity provides the first line of immunological defence. Therefore, for many diseases, protective immunity should ideally consist of antibodies or cells that are active at mucosal sites. Furthermore, we are now realising that enhanced methods of mucosal immunisation can induce both systemic and mucosal immunity, a highly desirable situation in terms of immunity. Induction of immunity at mucosal surfaces requires the administration of antigens directly to the mucosal site. However, efficient antigen delivery remains a problem for mucosal vaccines. Problems such as enzymatic destruction and/or inadequate mucosal contact and poor absorption can substantially decrease efficacy. To stimulate specific mucosal immune responses, it will be necessary to understand the criteria for optimal mucosal adjuvants as well as the most effective ways of expressing and presenting antigens using suitable delivery systems/strategies. For example, polymeric controlled-release technology, is one of the most studied systems, offering the

potential for meeting this need. Controlled release of antigens using polymer microspheres has already shown great promise in eliminating the need for booster shots for achieving successful parenteral immunisation. They also have been shown to induce potent humoral and cellular immune responses following oral, nasal, intratracheal and rectal administration.

There has been an increase in activity in the field of mucosal immunity in recent years. The present article presents a brief review of the mini-symposium, held recently in Stockholm during CRS meeting, on various aspects of mucosal immunisation relating to current developments in this area. Speakers of this symposium described a number of exciting approaches for inducing mucosal immune responses and the relative roles of mucosal immunity, systemic immunity, and protection from various diseases. Presentations included the role of adjuvants in the induction of immune responses. Co-chairpersons **Dr. Derek O'Hagan** and **Prof Maria-Jose Alonso** expertly hosted a session of high calibre podium presentations, intermixed with stimulating discussion from the floor.

The first invited speaker **Dr. J. Holmgren** from Göteborg University spoke in depth about Choleratoxin B (CTB), the non toxic receptor-binding moiety of cholera toxin, and its enormous potential as a mucosal adjuvant. He articulately outlined how it is possible, through conjugation of antigenic peptides and proteins to CTB, to stimulate strong local and systemic immunity through mucosal immunisation. The role of cytokines in the mediation of responses within mucosal associated lymphoid tissues was described. Whilst the existence of a common mucosal immune system dictates that concomitant stimulation of anatomically disparate mucosae is possible, Dr. Holmgrens findings indicate that strongest responses are induced in adjacent mucosal compartments. Interestingly, intra-nasal immunisation was found to induce strong mucosal responses not only in the lungs and upper respiratory regions, but also in the genital tract. He suggested such findings may well impact on the future development of vaccines for sexually transmitted diseases.

Systemic tolerance is a major factor which impedes the development of oral vaccines. Dr. Holmgren indicated that systemic tolerance induced through oral administration of CTB conjugated antigens could be used to prevent or reduce the intensity of certain allergic reactions or autoimmune diseases such as multiple sclerosis, type I diabetes and rheumatoid arthritis.

Disease states caused by certain species of toxin producing bacteria can be prevented through immunisation with non toxic forms of the toxin. **Dr. Rino Rappuoli** from Siena Italy described how it was possible, by producing a panel of pertussis and heat-labile enterotoxin mutants, to identify non-toxic molecules which elicit strong immunological responses after oral or intra-nasal administration and which will improve conventional vaccines, by serving as excellent mucosal adjuvants.

A common problem encountered in the development of mucosal vaccines is the inherently low immunogenicity of killed whole cell, or sub-unit, vaccines. **Dr. Peter Laing** from Peptide Therapeutics presented data showing how it is possible to utilise certain attenuated strains of *Salmonella* to induce both mucosal and systemic immunity to tetanus following oral administration. This has been achieved largely through increased knowledge regarding the regulation of bacterial genes *in vivo* in conjunction with identification of promoters which allow up regulation of heterologous antigen expression when a vector strain occupies a particular cellular compartment.

Dr. Bror Morein from Uppsala University in Sweden described a new generation of antigen delivery systems called Immunostimulating complexes (ISCOMS). These ISCOMS are nanoparticulates composed of cholesterol, a secondary lipid component and a triterpenoid extracted from the bark of Quilliaja saponaria, in addition to the antigen. The Quillaja extract has strong adjuvant properties resulting in efficient uptake of antigenic material into antigen presenting cells (APC's). Within APC's the spatial distribution of Quillaja adjuvantised antigens is unique in comparison to other adjuvants.

This is because Quillaja seems to promote the distribution of antigens to both the endosome/lysosome and cytosol. Hence antigen is presented in conjunction with both MHC class I, and MHC class II molecules leading to both CD4 and CD8 mediated responses. Dr. Morein discussed *in vivo* work in which immune responses following mucosal administration of ISCOMS were found to be influenced by co-administration of certain cytokines. For example, IL-5 was found to induce Th1 type responses if administered in conjunction with ISCOMS intra-nasally. Conversely, IFN-gamma and IL-2 were seen to increase serum Ig2a in experimental animals, indicative of a Th1 response. In light of this, Dr. Morein surmised that augmentation of antigen delivery systems with cytokines offers the potential to manipulate, and thus maximise, resultant immune responses.

The mini-symposium was concluded by **Dr. Derek O'Hagan** from Chiron Corporation, Emeryville, talking about the potential of microparticles as mucosal delivery vehicles. Certainly, there has been a substantial increase in our understanding of mucosal immunology and physiology over the last few years, as indicated above. Until recently it was commonly assumed that mucosal epithelias presented an all exclusive barrier to the passage of particulates into sub-epithelial compartments. However, there is now an increasing body of evidence to suggest that some degree of microparticulate translocation occurs routinely. This has led to initiatives for exploiting this phenomenon to deliver drugs and vaccines. After a concise summary of the mucosal immune system, histological data showing unequivocal evidence of translocation of fluorescent particles across the gastro-intestinal epithelium was presented by Dr. O'Hagan. The ability to induce humoral responses, both systemic and mucosal, alongside T-cellular activity following both oral and nasal administration of microencapsulated *Bordetella pertussis* antigens was presented in a series of slides depicting the findings of *in vivo* work. Importantly, mucosal application of this microencapsulated vaccine was shown to induce protection from challenge. The effect of various parameters on particle uptake and resultant immunological responses was outlined, rounded off with some highly stimulating discussion from an attentive audience. The progress made in terms of mucosal adjuvants in many different approaches presented during this symposium is very encouraging. Overall, an extremely informative morning of talks.

Oya Alpar

UKCRS Education Programme

The UKCRS is hoping to start an educational programme for scientists and other workers in the field of controlled release. The first initiative that the group would like to promote is the production of computer-based learning packages on specific technologies and techniques. These would serve as an introduction for Pharmacy undergraduates and postgraduates starting in fields of controlled release, other healthcare professionals and interested parties within the field. The packages would be developed using CAL/WWW techniques, which are already widely used in undergraduate courses and have also been used as training packages by companies in the fields of controlled release and pharmaceutical technology. The UKCRS is seeking sponsorship for production of such computer packages. Companies in specific fields could take the opportunity to promote their technologies or help in the production of packages explaining relevant techniques within the field. If you would like further information, please contact us at the UKCRS.

Mike Tobyn

UK Chapter to Expand to include Ireland

Negotiations to expand the UK chapter of the CRS to incorporate members from the Republic of Ireland have reached an advanced stage. The resulting joint chapter would be known as the UK-Ireland CRS, i.e. UKICRS.

The parent CRS society accepted the proposal for the incorporation of Irish members into the UK CRS at the recent Stockholm meeting. The necessary changes to the current UKCRS constitution to facilitate the expansion are currently being reviewed and it is hoped that a formal announcement of the inception of the new UKICRS will be made at the next national meeting, to be held at the School of Pharmacy, University of London, on 6th January 1998.

We look forward to the influx of energy and enthusiasm that the extended membership will undoubtedly bring, as well as the input of fresh ideas, both from the industrial and academic sector, which will prove invaluable in shaping future strategy at the committee level. A particularly exciting consequence of the formation of a UKICRS chapter is the possibility of holding an inaugural UKICRS meeting in Dublin. Many members will recall a highly successful conference on peptide delivery held in Dublin in September 1995 and organised by the ad hoc CRS Ireland committee. It is hoped that a conference with vaccines as a general theme will be organised under the auspices of the new joint chapter. The January meetings have become a highly regarded and successful addition to the conference calender, and with this proposed additional meeting, we can look forward to more state-of-the-art science, and of course some of that famous state-of-the-art Irish hospitality!

Anya Hillery

UKCRS on the Internet

In addition to being the first pharmaceutical organisation to develop a web site, the UKCRS can also take pride in being the first organisation to broadcast a pharmaceutical conference live on the Internet (see report of the January 1997 meeting). The UKCRS web pages have recently been updated and include all the latest UKCRS news. Information on the 4th UKCRS meeting in London will also be made available. A new mailing list has also been created for those of you interested in the activities of the UKCRS. To join the list simply go to our web page and select the mailing list. You can join/leave using a simple on-line form.You will be kept informed of UKCRS and CRS activities. There is also a controlled release discussion group available through the UKCRS site. The **NEW** URL (address) of the UKCRS page is:

http://www.pharmweb.net/ukcrs.html

Annual CRS Symposia Dates

June 21st - 26th, 1998, Las Vegas, Nevada, USA, *25th International Symposium on Controlled Release of Bioactive Materials*. This is the main International meeting of the CRS in 1998.

June 20th - 25th, 1999, Boston, Massachusetts, USA, *26th International Symposium on Controlled Release of Bioactive Materials*.

Other Meetings

September 15th - 18th, 1997, Scarborough, UK, *134th British Pharmaceutical Conference*

September 20th - 22nd, 1997, Beijing, China, CRS-CPA *Joint Symposium on Recent Advances in Drug Delivery Science and Technology*

September 24th - 26th, 1997, Seoul, Korea, KSP-CRS Joint Symposium on Recent Advances in Drug Delivery and Biomaterials

October 5th - 8th, 1997, La Jolla, CA, USA, *Conference on Formulations and Drug Delivery II*

November 17th - 19th , 1997, Los Angeles, CA, USA, *Biomaterials, Carriers for Drug Delivery, and Scaffolds for Tissue Engineering*

December 14th - 19th, 1997, Kauai, Hawaii, USA, *4th US-Japan Symposium on Drug Delivery Systems*

March 23rd - 25th, 1998, Damstadt, Germany, *Workshop on Role of the Biopharmaceutics Classification System and In Vitro-In Vivo Correlation in the Approval of Oral Drug Products*

Information on these and other conferences relevant to the field of controlled release may be found on the PharmWeb pages on the Internet at the following URL:

http://www.pharmweb.net/conferences.html

Joining the CRS

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