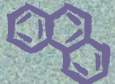




$$X^2 = \frac{\sum (O-E)^2}{E}$$



LONDON SCHOOL OF HYGIENE & TROPICAL MEDICINE

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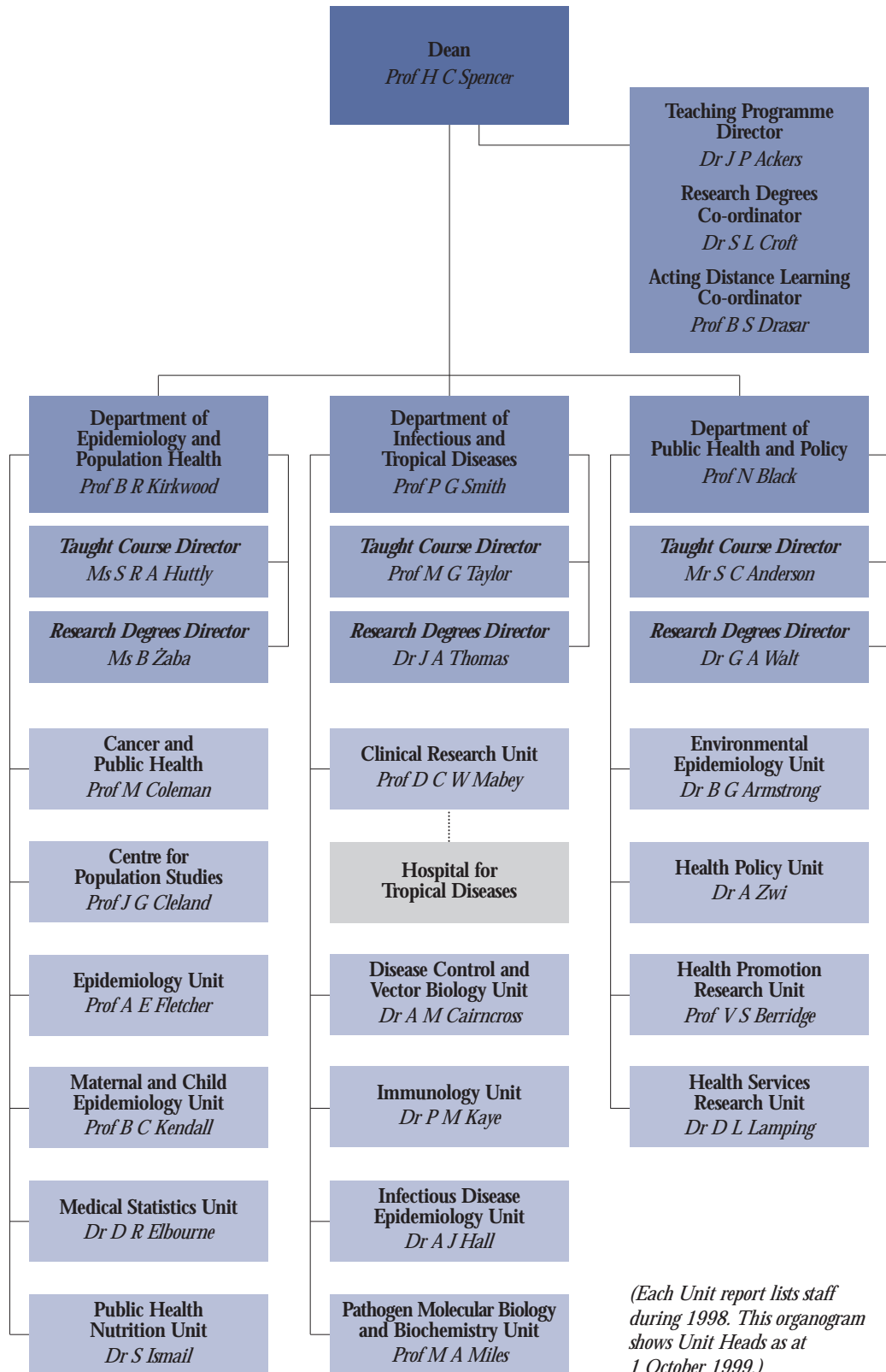
The mission of the London School of Hygiene & Tropical Medicine is to contribute to the improvement of health worldwide through the pursuit of excellence in research, postgraduate teaching, advanced training and consultancy in international public health and tropical medicine. To achieve this mission the School will enhance its role as:

- *Britain's national school of public health,*
- *a leading institution in Europe for research and postgraduate education in public health and tropical medicine, and*
- *an international centre of excellence in public health and medicine in developing countries.*

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# ACADEMIC MANAGEMENT STRUCTURE



## INTRODUCTION

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I am delighted to present this Research Report which describes the work of the London School for the calendar year 1998 and continues the layout found helpful by readers in previous years, where, for each Unit, there are lists of staff, funding sources and research degree students, a brief report summarizing the Unit's fields of interest followed by a selective account of results and progress in the last year, and a list of its publications. Cross-cutting themes are addressed through the indexes on pages 81-84. Research workers seeking doctoral or post-doctoral places may be interested to see which scientific and professional disciplines are to be found in each Unit (page 82) and policy makers from particular countries may wish to see which Units are collaborating with their scientists, carrying out collaborative studies in their countries, or providing doctoral training for their nationals (page 84).

Ever since the School first opened its doors as the London School of Tropical Medicine on 2nd October 1899, research has been at the heart of the School's mission. The depth and breadth of multidisciplinary research carried out as presented here is an indication of our continuing commitment to scientific excellence. Interested scientists are very welcome to contact Heads of Units or other staff directly if they need further information. A list of Unit Heads as at 1st October 1999 can be found opposite. As always, comments on how to make this report more useful to its readers will be most welcome.

*Professor Harrison Spencer*  
The Dean

September 1999





## DEPARTMENT OF EPIDEMIOLOGY AND POPULATION HEALTH

### HEAD OF DEPARTMENT

**Betty R Kirkwood** MA MSc DIC HonMFPHM

### DEPARTMENTAL ADMINISTRATOR

**Diana Harte**

### SECRETARY TO HEAD OF DEPARTMENT

**Rosie Infanti**

### ASSISTANT TO DEPARTMENTAL ADMINISTRATOR

**Gill Turner**

### COMPUTER SERVICES MANAGER

**Kate Outhwaite** BSc

### DEPARTMENTAL COMPUTING OFFICERS

**James Sanderson** BSc

**Andrew Reid** BA MSc

### ASSISTANT COMPUTING OFFICER

**Margaret Mutenga**

### COMPUTING TEACHING CO-ORDINATOR

**Judith Bailey** (until August 1998)

**Jill Szuscikiewicz** BA (from September 1998)

### COMPUTING TEACHING OFFICER

**Barbara Neville** BA MSc

### TEACHING SECRETARY

**Janette Costello**

### MSc COURSE SECRETARIES

**Nathalie Chatelain**

**Eve Kirunda-Sevume**

**Bettina Plettenberg**

**Rehka Soni** BA

**Val Vickery** BA

**Aruni Yapa** BA

### VISITING PROFESSORS

**Valerie Beral** MBBS MRCP

**Karen Dunnell** BSc MA HonMFPHM

**Stephen J Evans**

BA MSc MInstP MBCS FIMA FSS FIS HonMFPHM HonMRCR

**Richard GA Feachem**

CBE BSc PhD DSc(Med) FEng FICE FIWEM HonMFPHM

**John Fox** BSc PhD HonMFPHM

**Cesar Victora** MBBS PhD

### HONORARY SENIOR LECTURER

**Richard Wiseman** PhD

### EMERITUS PROFESSORS

**William Brass** CBE MA FBA

**Philip Payne** BSc FIBiol

**John Waterlow** CMG FRS MD ScD FRCP

The Department houses the largest group of epidemiologists, statisticians and medical demographers in Europe, together with nutritionists, social scientists and public health practitioners. It is engaged in an extensive programme of research on the health and nutrition of populations, or subgroups of populations (such as the elderly), in order to inform public health and social policy. This is carried out with a wide network of collaborators in low-, middle- and high-income countries.

The Department currently comprises just over 100 academic staff and almost 50 computing, administrative and secretarial staff. There is a thriving research degree programme enriching the academic life of the Department with about 50 students registered for higher degrees. Research degree students form an integral part of the six academic units. Research being conducted by them is summarized at the end of each Unit's entry.

Much of our research continues to build on the Bradford Hill tradition of well-designed aetiological studies and clinical trials. Increasingly, however, the Department is engaged in multidisciplinary research related to the development and evaluation of interventions, the design

and evaluation of public health programmes and policy analysis. A major development in this new tradition was the creation at the beginning of 1998 of the Cancer and Public Health Unit, bringing together the considerable expertise within the School in this area. This new Unit has a remit to carry out a broad programme of research ranging from descriptive epidemiology through to public health policy on cancer and other chronic diseases. It brings together three professors, Michel Coleman, Tony Swerdlow and Klim McPherson and their research groups, as well a new collaborative programme of work with the Institute of Cancer Research, led by Professor Julian Peto, who now holds a joint position between the School and the Institute.

Our research profile was further expanded in 1998 by the creation of two new senior posts, one in UK demography (with an emphasis on ageing) and another in child health (with an emphasis on health-seeking behaviour and quality of care related to the WHO/UNICEF Integrated Management of the Sick Child Initiative). We were most fortunate to recruit Dr Emily Grundy to the former as Reader in Social Gerontology (Centre for Population Studies) and Dr Carl Kendall to the latter as Professor of Medical Anthropology & International Health (Maternal



and Child Epidemiology Unit). In addition the Public Health Nutrition Unit has been enhanced by the arrival of Dr Andrew Prentice's MRC International Nutrition Unit.

Considerable methodological expertise in the Department means that our substantive research is underpinned by the development of new or refined methodologies in epidemiology, medical statistics, demography and intervention-related research. We have recently started a new MRC co-operative grouping on 'a life courses approach to studying disease'. This builds substantially on existing successful research, but the wider collaboration is extending it in innovative ways and is likely to lead to

major new insights and methodological development. We also received support from the School's Academic Initiative Fund to expand work in clinical trials from its current emphasis on cardiovascular diseases to a range of areas such as perinatal medicine, asthma and HIV.

We are delighted that SmithKline Beecham offered to fund a new Chair in Biostatistics, and most fortunate to have recruited Professor Mike Kenward to this post. He will join the Department in the summer of 1999, and will be building a programme of applied methodological work focusing on issues in the analysis of longitudinal data and missing values.



## CANCER AND PUBLIC HEALTH UNIT

<b>Michel Coleman</b> BA BM BCh MSc MFPHM	Professor & Head of Unit	<i>Epidemiologist</i>	<b>FUNDING BODIES</b> British Diabetic Association BUPA Foundation Cancer Research Campaign Civil Aviation Authority Commission of the European Communities Department of Health Foundation for Children with Leukaemia International Life Sciences Institute Medical Research Council NHS Executive
<b>Klim McPherson</b> MA PhD HonMFPHM FMedSci	Professor	<i>Epidemiologist</i>	
<b>Julian Peto</b> MA PhD	Professor	<i>Epidemiologist</i>	
<b>Anthony Swerdlow</b> BM BCh MA FFPHM PhD DM	Professor	<i>Epidemiologist</i>	
<b>Bianca De Stavola</b> BSc MSc PhD	Senior Lecturer	<i>Statistician</i>	
<b>Isabel dos Santos Silva</b> MD MSc DipPH&TM PhD	Senior Lecturer	<i>Epidemiologist</i>	
<b>Elaine Meilahn</b> MPH DrPH	Senior Lecturer	<i>Epidemiologist</i>	
<b>Craig Higgins</b> BSc MSc	Lecturer	<i>Statistician</i>	
<b>Michael Jones</b> BSc MSc	Lecturer	<i>Statistician</i>	
<b>Punam Mangtani</b> BSc MBBS DCH MRCP MRCGP MSc MD	Lecturer	<i>Epidemiologist</i>	
<b>Dee Bhakta</b> SRD RD	Research Fellow	<i>Dietician</i>	
<b>Eldonna Boisson</b> MSc BSc	Research Fellow	<i>Demographer</i>	
<b>Annie Britton</b> BA MSc	Research Fellow	<i>Epidemiologist</i>	
<b>Susan Laing</b> MA PhD	Research Fellow	<i>Epidemiologist</i>	
<b>Geraldine Leydon</b> BA MA	Research Fellow	<i>Sociologist</i>	
<b>Alison Metcalfe</b> BSc	Research Fellow		
<b>Leena Sevak</b> BSc MSc	Research Fellow	<i>Nutritionist</i>	
<b>David Wonderling</b> BA MSc	Research Fellow	<i>Economist</i>	
<b>Fiona Barber</b> SRN	Research Nurse		
<b>Pip Murnaghan</b> OND RGN RNT MPhil	Research Nurse		
<b>Maureen Swanwick</b> SRN NRT	Research Nurse		
<b>Laurent Chenet</b>	Research Assistant		
<b>Gerhart Knerer</b> MA MSc	Research Assistant	<i>Statistician</i>	
<b>David Mayer</b> BSc MSc	Research Assistant		
<b>Bonita Peachey</b> BA	Research Assistant		
<b>Minouk Schoemaker</b> BSc MSc	Research Assistant	<i>Statistician</i>	
<b>Janette Dobbins</b> BSc MSc	Data Manager		
<b>Steve Bond</b>	Computer Officer		
<b>Debbie Carson</b> BA	Computer Staff		
<b>Zongkai Qiao</b> MPH MSc	Computer Officer		
<b>Rakhi Kabawala</b>	Project Interviewer		
<b>Nidhi Khurana</b> BCOM(Hons) MCOM	Project Interviewer		
<b>Christine Johnson</b>	Research Clerk		
<b>Ha Nguyen</b>	Research Clerk		
<b>Joyce Nicholas</b>	Research Clerk		
<b>Teresa Thorpe</b>	Research Clerk		
<b>Katie Andrew</b>	Project Secretary		
<b>Christine Brandon Jones</b>	Secretary		
<b>Evelyn Middleton</b>	Programme Secretary		
<b>Pascale Grosclaude</b>	Visiting Research Fellow	<i>Tarn Cancer Registry, France</i>	
<b>Alexandre Pitard</b> PhD	Visiting Research Fellow	<i>Université de Franche-Comté, France</i>	

The Cancer and Public Health Unit was formed on 1 January 1998 to provide a focus for the School's research on public health problems due to cancer and to other chronic diseases, particularly diabetes and coronary heart disease (CHD).

### TRENDS IN CANCER INCIDENCE, MORTALITY AND SURVIVAL

In collaboration with the Office for National Statistics (ONS) and with funding from the Cancer Research Campaign, Michel Coleman has co-ordinated a major study on cancer survival trends by material deprivation in England and Wales

over the period 1971-95 among almost three million patients. A book and a CD-ROM with the data and the findings were published (COLEMAN, MP et al. *Cancer survival trends in England and Wales 1971-1995: deprivation and NHS region*. London: The Stationery Office, 1999. *Studies in Medical & Population Subjects no.61*. ISBN 0-11-621031-1). Survival rates in the 100 Health Authorities are included among NHS outcome indicators and the stability of ranking and the effects of spatial auto-correlation are being examined. We have also made a major contribution to the EURO CARE study of cancer treatment and survival, which



provides comparisons of cancer survival across 17 European countries. A monograph with the main findings from this international study will be published in 1999. We have also conducted a major analysis of long-term trends in cancer incidence and mortality in the UK and a book with the major findings is being prepared in collaboration with Sir Richard Doll (Oxford University).

We have developed a computer algorithm to ascribe ethnicity, religion and region of origin of South Asians, the largest minority ethnic group in Britain, on the basis of their names. The dictionary contains about 20,000 first names and surnames. The algorithm performed well on preliminary validation. It is now being used in mortality and cancer registration data to examine the patterns of illness between the host and the migrant population in relation to their varying experience of environmental factors.

#### REPRODUCTIVE-RELATED CANCERS AND OTHER CHRONIC DISEASES IN WOMEN

The Unit has been studying how reproductive factors and sex hormones relate to chronic disease risk, in particular female-reproductive cancers and CHD in women. We contributed to a population-based cohort study of cancer risk in the relatives of women with breast and ovarian cancer and investigated the causes of breast (and testicular) cancer in a large population-based study of cancer in twins. We are now co-ordinating a national case-control study of the risk of second cancers of the uterus, ovary, large bowel and liver following tamoxifen treatment; a prospective study on the role of oestrogen metabolism in the risk of breast cancer; and a case-control study of contralateral breast cancer in young women. We are also conducting a case-control study to examine the protective effect of fruit and vegetables (mediated by phyto-oestrogens) on breast cancer risk in women of South Asian ethnicity.

We have been exploring the hypothesis that sex hormone levels underlie the difference in CHD risk between men and women, through population-based studies of exposure to sex hormones. In a cohort study of women from Guernsey, we are relating CHD mortality over a 20-year follow-up to endogenous androgen levels. We have also been involved in a study of bone density and hormone levels in women.

#### FOLLOW-UP OF CLINICAL COHORTS

The Unit is involved in following large patient cohorts, for the long-term effects of the diseases and their treatments on the risks of unwanted complications. We have reported on risks of testicular cancer several decades after orchidopexy and hormonal treatments for cryptorchidism, and second malignancy after Hodgkin's disease, as well as the long-term follow-up of patients with congenital adrenal hyperplasia and insulin-treated diabetes. A cohort of patients who underwent cardiothoracic transplantation, and large cohorts of patients with various genetic disorders and other studies are close to fruition. A long-term cohort study of 24,000 women treated

variously for menorrhagia is being set up.

#### HEALTH EFFECTS OF EXPOSURE TO IONIZING AND NON-IONIZING RADIATION

Our research on ionizing radiation has involved both internally deposited radionuclides – from Thorotrast in a Portuguese population and from plutonium in nuclear workers in the UK – and external radiation, in nuclear workers and in cancer patients. We also examined the influence of pigmentation on melanoma risk, worked on the dosimetry of ultraviolet radiation exposure, and participated in various case-control studies of melanoma.

#### HEALTH SERVICES RESEARCH

The information services for cancer patients and their families are being studied in collaboration with Cancer BACUP, to evaluate local services and improve understanding of cancer patients' information needs. We are also carrying out an audit of advice given at 27 cancer genetic services throughout the UK with follow-up of patients seen. We are beginning a national case-control study of cervical cancer to assess the influence of screening history on the risk of death. We have also completed a study of intensive care in the UK, and estimated the attributable mortality associated with the refusal to admit appropriately referred patients. The efficiency of intensive care in Colombia is being studied.

#### METHODOLOGICAL WORK

Unit staff are tackling the methodology of survival analysis, the bias caused by migration in case-control studies of prenatal factors for later disease, and statistical methods for the analysis of repeated exposure measurements in longitudinal studies. We have been investigating the possible role of patient preferences in assessing the effect of treatments, quantifying the extent to which randomized controlled trials might be misleading if such preferences were to affect the outcome. The Unit uses models to predict the health effects, including cancers, of hormone replacement therapy (HRT) and alcohol use. We have also reviewed health-related theoretical models for understanding the determinants of behavioural change. Isabel dos Santos Silva published a textbook on methodological principles in cancer epidemiology, with the International Agency for Research on Cancer.

#### OTHER RESEARCH

We are carrying out studies: of trends in mortality from Creutzfeldt-Jakob disease (CJD); on the possible mis-certification at death of CJD in the past; on drink driving; on alcohol policy in Europe; on the prognosis in primary biliary cirrhosis; on the assessment of foetal compromise by Doppler; on the diet of populations in Britain; on the cost-effectiveness of hepatitis B vaccination; and on the notification of tuberculosis in England and Wales.

#### FROM RESEARCH TO POLICY

We have contributed to debates on the future of public health



in the UK; to the Acheson Inquiry on Inequalities in Health, to the Chief Medical Officer's review of the public health function; and to the development of multidisciplinary public health. We have helped to set up the UK Health Policy Group at the School, to bring together researchers from all Units with an interest in the application of public health

research in the policy arena. Klim McPherson has made a contribution to the assessment of different methods of training and accreditation of specialists in public health in the UK, in collaboration with various national bodies and the NHS executive. An evaluation of the EC Europe Against Cancer programme was also co-ordinated in the Unit.

### RESEARCH DEGREE STUDENTS

**Dee Bhakta** (UK). Dietary intake, nutritional status and chronic diseases in South Asian and British women.

**Dympna Edwards** (UK). Variations in head and neck cancer services.

**Shin Lan Koong** (Taiwan). Evaluation of cervical screening policy in Taiwan.

**Elena Riza** (Greece). Determinants of mammographic parenchymal patterns and implications for breast cancer aetiology: a study in Northern Greece (Ormylia mammography screening programme).

**Diane I. Stockton** (UK). Cancer survival — understanding geographic and social variation.

**Gabriella Torres Mejia** (Mexico). Influence of lifestyle and nutritional factors on women's chronic disease.

**Regina A Winkelmann** (Germany). Cancer registration in the former USSR.

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## CENTRE FOR POPULATION STUDIES

<b>John Cleland</b> MA	Professor & Head of Unit	<i>Demographer</i>	<b>FUNDING BODIES</b> Department for International Development (DIFD)  Department for Social Security  Family Care International  Economic and Social Research Council  Family Policy Studies Centre  Ford Foundation  Mellon Foundation  Nuffield Foundation  Population Council  Rockefeller Foundation  The Wellcome Trust  World Health Organization
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<b>Emily Grundy</b> MA MSc PhD	Reader	<i>Demographer</i>	
<b>Fatima Juarez</b> BSc MSc PhD	Senior Lecturer	<i>Demographer</i>	
<b>Ian M Timæus</b> MA MSc(Econ) PhD	Senior Lecturer	<i>Demographer</i>	
<b>Basia W Zaba</b> BSc MSc	Senior Lecturer	<i>Demographer</i>	
<b>Sarah Castle</b> BA PhD	Lecturer	<i>Demographic Anthropologist</i>	
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<b>Andrew Sloggett</b> MSc MRPharmS	Lecturer	<i>Demographer</i>	
<b>Brent Wolff</b> MHS MA PhD	Lecturer	<i>Sociologist</i>	
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<b>Martine Collumbien</b> MSc(Agric) MSc	Research Fellow	<i>Demographer</i>	
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<b>Masuma Mamdani</b> BA MPH	Research Fellow	<i>Epidemiologist</i>	
<b>Nicola Shelton</b> BSc Dip StatsComp	Research Fellow	<i>Population Geographer</i>	
<b>John Simons</b> BA BSc(Econ)	Honorary Research Fellow	<i>Sociologist</i>	
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<b>Evelyn Dodd</b> BA	Unit Secretary		
<b>Huyette Shillingford</b>	Secretary		
<b>Rekha Soni</b> BA	Course Secretary		

The Centre is an interdisciplinary unit focusing on the measurement and explanation of population trends, and their consequences, in both developed and developing countries. The recruitment of Emily Grundy, Reader in Social Gerontology, has strengthened research activities in UK demography. Close links with the Family Policy Studies Centre ensure rapid dissemination of recent research results and their policy implications. A DFID programme grant supports much of the Centre's work on population and reproductive health in developing countries, with a particular focus on sub-Saharan Africa and South Asia.

### POPULATION AND HEALTH IN THE DEVELOPED WORLD

Much of the completed work of the Centre staff working on developed countries concerned family and household circumstances and change across the life course, particularly in relation to health and well-being. An investigation by Andy Sloggett with Professor Glyn Lewis (University of Cardiff) of the ONS Longitudinal Study revealed that the risk of suicide was more strongly associated with lack of job security than with other socio-economic variables. Approximately 7% of suicides may be attributable to job insecurity, a figure which rises to nearly 13% for younger men.

In work with Glyn Lewis and Dr S Weich (Royal Free Hospital), Andy Sloggett used the British Household Panel

Study to investigate the link between common mental disorders and the number of social roles (worker, spouse, carer, etc.) which men and women hold. The hypothesis that common mental disorders are associated with unusually high or low numbers of social roles had some support but this did not explain the higher prevalence of common mental disorders amongst women.

Work on deprivation, with Professor H Joshi (Institute of Education), again made use of the ONS Longitudinal Study. Several adverse or 'inauspicious' life events (low birthweight, teenage birth, sole registered birth) showed strong associations with an areal index of deprivation. In most instances, but not all, personal or household factors outweighed the ecological measure in explaining incidence. The work demonstrated that, although personal factors seem overriding, census-based measures of local area deprivation can help identify not only mortality differentials but a variety of other poor outcomes. The incidence of teenage pregnancy and single-registered births appeared particularly sensitive to the social profile of an area.

Lynda Clarke, in collaboration with Dr E Cooksey (Ohio State University) undertook a comparative analysis of the socio-demographic profiles of fathers, and determinants of absent fatherhood in Britain and the United States. They found that, although fathers are on average younger in the



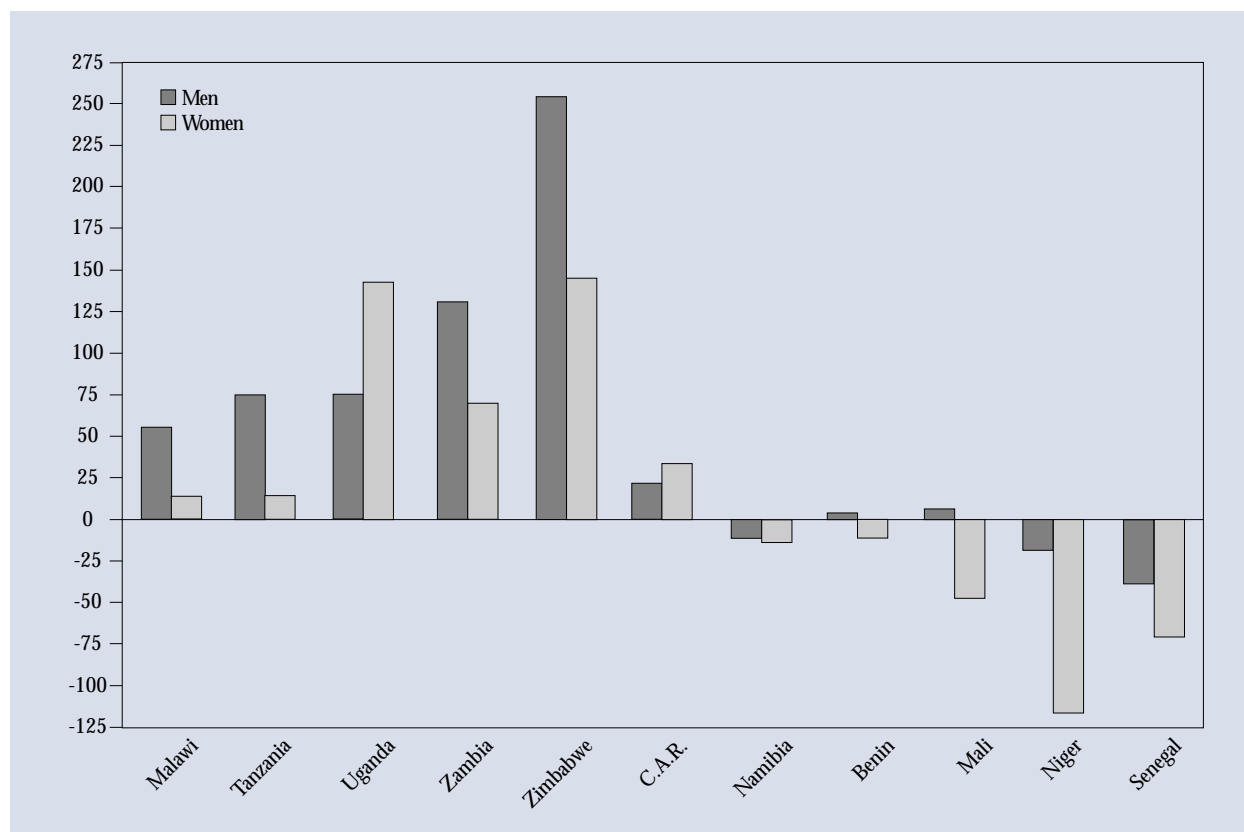
USA than in Britain, predictors of fathers' residency with their children are remarkably similar in the two countries. In both countries, the strongest predictor of a father's absence is the parents' relationship to each other at the time of the child's birth. Clarke also continued collaborative work with colleagues from City University on the effects of demographic change on the well-being of children and with the Family Policy Studies Centre on trends and patterns of childlessness in Britain. Analyses of longitudinal data from Britain and the USA showed an association between family type and child development in both countries. However, in the USA this association was stronger. Associations between household type, household change, migration and health at the other end of the age spectrum were the focus of some of Emily Grundy's work. Using data from the ONS Longitudinal Study she examined transitions between different types of household in 1971-81 and 1981-91. In the second decade, higher proportions of the very old moved to institutional care, while the proportion moving to join relatives was lower than in 1971-81. Regional differences in household type and household transitions diminished over the period considered. Other work included overviews of health status in later life and further consideration, with Ann Bowling, of the relationship between social networks and health.

#### MORTALITY IMPACT OF AIDS IN AFRICA

In most of sub-Saharan Africa, the coverage of routine systems for the registration of deaths is very low. Thus, it is difficult to measure the impact on mortality of the HIV

epidemic in this region. Estimates and projections produced by United Nations (UN) agencies and others indicate that massive declines in life expectancy have occurred in the more severely affected countries during the last decade. Until now, it has only been possible to document this directly for a few relatively small populations that have been the subject of intensive research. Recently, however, a range of survey and census data has begun to become available that can potentially measure mortality trends up to the early- or mid-1990s in at least some national populations in Africa. In response, in part, to requests from the UN Population Division, UNAIDS and the World Bank, the Centre has undertaken a series of studies to analyse these data.

The results demonstrate that the downward trend in adult mortality that existed in Eastern and Southern Africa until the 1980s has been reversed. In countries where HIV became prevalent by the late-1980s, massive rises in mortality occurred by the mid-1990s. In general, the rise in adult men's mortality has been at least as large as that in women's mortality. Adult death rates doubled or tripled between the 1980s and mid-1990s in Uganda, Zambia, and Zimbabwe. By 1996, 60 per cent of those Zambians who survived to age 15 could expect to die before age 60. Mortality has also risen substantially in the other Eastern and Middle African countries for which data exist but not in Western Africa. This geographical contrast, in combination with the finding that young adults aged 20-39 have been affected most where mortality has risen, makes it clear that the increase in adult



Percentage change over 6 years in adult death rates in 11 African countries, 1980s - 1990s. (C.A.R. = Central African Republic).



mortality is accounted for by AIDS deaths. This research also revealed that under-five mortality is stagnant or rising in several African countries. In most of these countries, this adverse trend is associated with the spread of HIV. In a few countries such as Nigeria and Zambia, however, infant and child mortality began to increase too early in the 1980s for this to be attributable entirely to HIV.

### FERTILITY AND FAMILY PLANNING IN PAKISTAN

With funding from DFID, staff have assisted the National Institute of Population Studies in Islamabad in carrying out and analysing a nationally representative demographic survey. Though Pakistan still records much higher fertility than most other South Asian countries, the level of childbearing has now fallen to about 5.5 births per women from an earlier level of 7.0 births. One reason for this decline is rising age at marriage. In 1951 the mean age at marriage for females was 16.9 years. By 1996-7 it had increased to 22.0 years. Increased contraceptive use is the second direct cause. The survey estimated that 24 per cent of married couples are now

practising a method, up from 12 per cent in the early 1990s. Contrary to the stereotype that husbands are hostile or indifferent to family planning, two of the three most commonly used methods in 1996-97 were condoms and coitus interruptus. Megan Douthwaite undertook an intensive small scale-study of couples who practised the latter and found that the decision to use withdrawal was typically a joint one between husband and wife. Neither sex dominated the initiation of use. The main reason for use was the desire to prevent pregnancy without running the risk of side effects that were associated with modern contraceptive methods. Secondary reasons included convenience and privacy. One of the most intriguing findings of the study was the absence of a commonly understood term to describe coitus interruptus. A total of 17 different words or phrases were encountered in the course of the study. This lack of widely-understood terms suggests that the method is not a familiar element of sexual culture in Pakistan but rather that widespread resort to coitus interruptus is relatively recent and not discussed except within marriage.

### RESEARCH DEGREE STUDENTS

**Nurul Alam** (Bangladesh). Child morbidity and health service use in rural Bangladesh.

**Paul Armstrong** (UK). Some are chosen, some are left! Who waits for elective surgery and why?

**Virgile Capo-Chichi** (Benin). Birth spacing and contraception in Cotonou, Benin.

**Susan Hunter** (UK). Fertility effects of HIV: implications for prevalence measurement based on antenatal surveillance.

**Mashbileg Maidrag** (Mongolia). Adolescents' sexual behaviour in Mongolia: knowledge, attitudes and practices.

**Cicely Marston** (UK). Teenage sexuality in Mexico.

**Tom Moultrie** (South Africa). Fertility among urban residents and migrants in South Africa.

**Rose Nathan** (Tanzania). Fostering and orphanhood in south-east Tanzania.

**Lewis Ndhlovu** (Zimbabwe). Quality of family planning services and their relationship to facility utilization.

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Boisson E. (UK) *Sexual behaviour and bias in HIV prevalence estimates based on pregnant women*. (PhD), 1998.

Muhwava W. (Zimbabwe) *Fertility decline in Zimbabwe*. (PhD), 1998.

Taylor H. (UK) *Child work and school attendance in urban India*. (PhD), 1998.



## EPIDEMIOLOGY UNIT

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<b>David A Leon</b> BA PhD	Reader	<i>Epidemiologist</i>	
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<b>Joceline Pomerleau</b> BSc MSc PhD	Lecturer	<i>Epidemiologist</i>	
<b>Gail Davey</b> MB BChir MRCP MD	Honorary Lecturer	<i>Epidemiologist</i>	
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<b>Julia Stowe</b>	Clerical Assistant		
<b>Janet Sullivan</b>	Clerical Assistant		
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Research activities in the Epidemiology Unit are diverse. Most of the research is of an aetiological kind (ranging from genes to personal behaviours and exposures, to national diets and drinking behaviours, to global climatic patterns); some assesses preventive interventions; some entails population health risk assessment; and some assesses aspects of health care. Inequalities in health is a theme spanning much of this research.

## FOETAL ORIGINS OF ADULT DISEASE

The portfolio of projects on the early origins of adult disease built up in the Unit continues to grow. David Leon and colleagues in the Unit, the Cancer and Public Health and Public Health Nutrition Units has established an MRC Co-operative Group on life course and trans-generational influences on disease risk. This multidisciplinary co-operative aims to address the influence of exposures operating across the life course and between generations and diseases and their



socio-economic variation. A new project from the Co-operative Group will revitalize a cohort of 13,000 Aberdeen schoolchildren born in the 1950s to study life-course influences on birth outcome and health.

Elizabeth Hall, David Leon, Paul McKeigue and Tony McMichael have been studying coronary artery calcification in relation to size at birth and ethnicity in collaboration with the Royal Brompton Hospital. Links with Uppsala, Sweden have continued to bear fruit, with Ilona Koupilova, David Leon and Paul McKeigue showing that blood pressure and known cardiovascular risk factors measured in middle age do not mediate the association between size at birth and cardiovascular mortality. Further work with the Swedish collaborators includes an analysis of blood pressure in relation to size at birth in 160,000 Swedish conscripts and a study of maternal affects on childhood blood pressure and endothelial function.

#### EPIDEMIOLOGY OF AGEING

Another major programme of work focuses on the elderly, and includes studies of screening, nutritional epidemiology, ophthalmic epidemiology and health inequalities. The MRC Trial of Assessment and Management of over-75s in the community is a randomized trial in 106 general practices (some 40,000 elderly people) which aims to evaluate universal versus selective screening and a multidisciplinary geriatric team versus a primary care team. The main outcomes of the trial are mortality, hospital and institutional admissions, quality of life and economic data on use of health services. Astrid Fletcher, David Leon and Elizabeth Breeze, in collaboration with University College London (UCL) and the Clinical Trials Unit at Oxford have recently completed a re-survey of the Whitehall cohort (9000 men) and shown the persistence of social class inequalities on morbidity in old age.

A variety of studies on nutrition is being undertaken, including a detailed nutrition and physical activity assessment in a sample of 2000 patients in the MRC Elderly Hypertension Trial; and a case-control study of diet and UV exposure as risk factors for cataract in Spain (conducted by Maria Pastor).

#### REPRODUCTIVE HEALTH

Pat Doyle, Noreen Maconochie and the reproductive epidemiology group are conducting a number of projects. Analyses of the Nuclear Industry Family Study are nearing completion; outcomes of interest include foetal death, congenital malformation and childhood cancer. A large study of reproductive outcome and child health among 53,000 UK veterans of the 1991 Gulf War and a similarly-sized comparison group is in the data-collection phase. Other ongoing studies include the follow-up of women treated for infertility, and the resulting children, and the investigation of variation in the sex ratio. A study of reproduction in dry cleaning workers is now complete. Women who operated dry cleaning machines at the time of their pregnancy had an approximately 50% excess

risk of miscarriage compared to women who did not operate machines but did similar work. Work on low birthweight and infertility in this workforce is ongoing.

#### PSYCHIATRIC EPIDEMIOLOGY

Martin Prince's main research area is in the aetiology and prevention of late-life mental disorder. The Gospel Oak Study in North London has been a valuable research resource in understanding the relationship between depression, disablement and handicap in later life. Martin Prince, in conjunction with Scott Weich and others from the Royal Free Hospital are evaluating the effects of Camden Council's regeneration project on mental health and quality of life.

The 10/66 group established by Martin Prince is planning pilot studies on the methodological problems associated with dementia diagnosis in low education populations and care arrangements for people with dementia in a range of international settings. Data from the 12-year follow-up of the MRC Elderly Hypertension Trial cohort explores the interaction of genetic and environmental risk factors in the aetiology of dementia. At the other end of the age spectrum, Kumari Galbodi-Liyanage is examining the relationship between nurturing and behaviour disorder in pre-school children in East London.

#### ETHNIC VARIATION IN DISEASE RISK

Paul McKeigue and colleagues are studying the interactions between genes, metabolism and behaviour that underlie ethnic variation in rates of diabetes and cardiovascular disease. They have developed a novel method to measure whole-body nitric oxide production, and are using this to study the metabolic basis of hypertension in West African and Afro-Caribbean people. Paul McKeigue has devised a novel approach to mapping genes that underlie ethnic differences in disease risk. Collection of hypertensive families for a study based on this design is under way in Trinidad. Mariam Molokhia is studying the relationship of systemic lupus erythematosus to non-African admixture in people of West African descent in Trinidad.

#### ENVIRONMENT, CLIMATE CHANGE AND HUMAN HEALTH

With colleagues at St George's Hospital and UCL, Tony McMichael has analysed the impact of air pollution patterns in London on short-term variations in deaths, hospital admissions/visits and GP consultations. Formal quantitative risk assessments are now being conducted, to aid policy-making.

The prospect of global climate change poses an unusual challenge to public health scientists: how best to forecast the likely population health impacts? A project funded by the UK government has begun to assess the impact of climate change on malaria, dengue, schistosomiasis, and thermal stress. This work, based on the development, validation and use of mathematical modelling, is being done in collaboration with



colleagues at the University of Maastricht and the Jackson Environment Institute, UCL.

Tony McMichael and Sari Kovats have contributed to several reports of the UN's Intergovernmental Panel on Climate Change Working Group II. Tony McMichael is currently the co-Convening Lead Author of the chapter on Human Health for the IPCC's Third Assessment Report. Sari Kovats has co-authored reviews on the potential health impacts of climate change in Europe for the WHO-European Centre for Environment and Health and an EU-funded project, and has co-authored a report for WHO on the health impacts of El Niño in developing countries.

## HEALTH IN EASTERN EUROPE

The epidemiological work of the European Centre on Health of Societies in Transition (ECOHST) continues apace. Substantial socio-economic differences in mortality in Russia both before and after the collapse of the Soviet Union in 1991

have been described by David Leon in collaboration with colleagues from Moscow. Further studies of adult mortality in Russia and Estonia are under way.

Iлона Koupilová with colleagues from the Czech Republic and Estonia has studied social variation in birth outcome during the period of transition in these two countries. Iлона Koupilová also continues to work on the European Longitudinal Study on Pregnancy and Childhood, investigating the effects of social stress and support on health of children and parents in selected European countries.

Most recently ECOHOST has been undertaking a comparative study of injuries and violence among children in the former communist countries of Europe. Rates of mortality from these causes are two to three times higher than in the West and provide an important area for potential effective public health action.

## RESEARCH DEGREE STUDENTS

**Emily Banks (UK).** Prospective study of hormone replacement therapy and breast cancer.

**Jenny Evans (UK).** Risk factors for age-related macular degeneration.

**Kumari Galboda-Liyanage (Sri Lanka).** Effect of parenting style on emotional/behaviour disturbance of pre-school children.

**Susan Morton (New Zealand).** Biological and social determinants of reproductive outcome and inter-generational study of Aberdeen women.

**Maria Asuncion Pastor Valero (Spain).** The contribution of nutritional intake, sunlight exposure and the history of diarrhoeal illness to the aetiology of cataract.

**Katalin Veress (Hungary).** Epidemiological approaches to monitoring, defining correlates and prevention of drug abuse in Hungary.

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- Al-Mahroos F (Bahrain) *Prevalence of diabetes and coronary heart disease risk factors among Bahrainis in Bahrain*. (PhD), 1998.
- DAVEY G. (UK) *Exercise and omega-3 fatty acids supplementation in insulin resistance in South Asians and Europeans*. (University of Cambridge MD), 1998.



## MATERNAL AND CHILD EPIDEMIOLOGY UNIT

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<b>Angela Vega</b> BA	Unit Secretary		

Multidisciplinary and international collaborative research involving epidemiology and the social and behavioural sciences to improve maternal and child health is the focus of work in the Unit. Staff working in the Population and Reproductive Health Programme are an internationally recognized source of research and policy for programmes attempting to reduce maternal mortality and improve childbirth for all women. Child health researchers work closely with the World Health Organization's Integrated Management of Childhood Illness programme in defining new interventions, enhancing care seeking and evaluating outcomes. Traditional strengths of the Unit in the development and quantitative evaluation of interventions are now being integrated with qualitative research tools to improve the appropriateness and effectiveness of interventions and to improve provider performance and the quality of care.

### POPULATION AND REPRODUCTIVE HEALTH PROGRAMME

The DFID-funded four-year Population and Reproductive Health Programme ended in March 1999. It brought together two groups at the School -- one working on population and family planning and the other on maternal health -- together with a group at Liverpool specializing in adolescent health issues. Programme staff generated well over 100 papers and reports on a broad range of topics. This brief selective summary of achievements is restricted to the outputs

of the maternal health group in London.

The maternal health component focused on assessing the effectiveness of specific elements of maternity care. A successfully completed randomized controlled trial looking at the effectiveness of bednets and malaria chemoprophylaxis in preventing severe anaemia in primipara in Kenya showed that while bednets had no effect on preventing severe anaemia in women, sulfadoxine-pyrimethamine in the second and third trimesters of pregnancy was successful in reducing severe anaemia by 39%. This latter result has been adopted as policy in Kenya and widens poor women's access to effective care. We also studied the effect of post-abortion contraceptive counselling on contraceptive uptake in Brazil, and showed that while counselling improved knowledge of contraceptive methods, there was no impact on uptake of contraception or on subsequent pregnancy rates. A follow-up study looked at widening access to reproductive health services by introducing an emergency contraceptive service, which is likely to be more suitable to the needs of women in unstable relationships.

The programme also looked at ways of determining the health impact of comprehensive maternal health services. Examples of research informing the latter are: evaluating a government upgrading of district maternity services in South Kalimantan, Indonesia; monitoring an anaemia-prevention programme in Malawi; developing 'near-miss' indicators for



maternal mortality in Benin; and exploring methods of assessing quality of obstetric care. Results from these studies are being finalized. Our overall experience within the Maternal Health Programme over the last decade is published in 'Lessons Learnt'. A new five-year programme in maternal health begins in 1999.

### NEAR-MISS AUDITS

Staff in the Population and Reproductive Health Programme are conducting a study entitled 'Hospital near-miss enquiries as a strategy to improve the quality of obstetric care in Benin, Côte d'Ivoire and Morocco', funded by the European Commission and the Department for International Development. The overall aim of this study is to develop, implement and evaluate a new strategy to monitor and improve the quality of obstetric care in referral hospitals in Benin, Côte d'Ivoire, Morocco and Ghana. This strategy is based on the identification of substandard care and avoidable factors related to near-miss obstetric events in referral hospitals, and on the participation of all those concerned in the selected hospitals and in the policy arena. It involves: setting-up a Near-Miss Enquiry Committee in each of the three countries to facilitate the development and application of the near-miss enquiry tool; developing a quality of care framework adapted to the local contexts, for measuring standards of care through the study of near-miss events; applying the new enquiry tool in 6 referral hospitals with detailed multidisciplinary case studies of a sample of near-miss events and a quantitative analysis of routine medical records for all near-miss cases; identifying realistic targets based on the enquiries' findings; and measuring progress towards selected targets. The success of the enquiries in bringing changes in the quality of care provided (from both a clinical and policy perspective) and in promoting health providers awareness and accountability will then be evaluated.

### CAESAREAN SECTION

Births by Caesarean section have increased in many countries, Brazil being particularly notable, to levels higher than necessary to ensure mothers' and infants' health. The underlying factors are many and complex, ranging from practice and attitudes of health service providers, organization of maternity services to women's preferences.

A study in a large public maternity hospital in southern Brazil included observation in the delivery room, in-depth interviews of obstetricians and a survey of women after their deliveries. Apart from absolute medical indications, women most likely to have a Caesarean tend to be older, with either a previous Caesarean or having their first birth, with previous delivery experiences favouring Caesarean, or otherwise pre-disposed to a Caesarean, who take steps during pregnancy to ensure one, or who seek admission for delivery early. Physicians' attitudes are crucial for the performance of Caesarean section and vary among individual obstetricians. The maternity environment appears to induce anxiety, with

an interventionist approach and value placed on delivery 'on time'. The study helped define the need for educating physicians and policy dialogue, and more preparation and information for women in pregnancy.

### WORKING WITH PROVIDERS IN CENTRAL ASIA

Staff in the Population and Reproductive Health Programme are also working directly with providers to improve obstetric practice. In collaboration with HealthProm, a London-based NGO, senior obstetricians and neonatologists in Uzbekistan are involved in an initiative to manage the introduction of more cost-effective primary care. Some physicians had resisted this change, fearing hospital closure and job insecurity. One barrier to change was an elaborate system of medical standards (Prikaz) that had been handed down by previous generations of obstetricians. The Prikaz — closely guarded and little disseminated — are applied by gatekeepers to punish physicians who adopt new practices. The goal of the project now is to engage gatekeepers and other physicians in Uzbekistan in developing flexible, evidence-based and cost-effective practices and guidelines that respond to the sweeping changes occurring in Uzbekistan.

### HYGIENE PROMOTION

The sanitary disposal of faeces is recognized as a key behaviour for promotion to prevent diarrhoeal diseases in young children, yet surprisingly little is known about faeces disposal practices, their determinants and feasibility for change. Phase 1 of this study used qualitative research methods to investigate these issues in a shanty town of Lima. The use of potties and the clearance of stools in situations where 'accidents' occur among the toddler age group, emerged as priority areas of behaviour. A micro-trial was conducted which indicated that change in these behaviours was both feasible and acceptable.

In Phase 2, a trial was undertaken in eight communities of the shanty town. Health centre personnel were trained in effective communication techniques and in the content of materials to promote hygiene. The latter included a motivational video in the style of a soap opera and illustrated pamphlets; these were very popular with staff and the target population.

Difficulties were encountered in achieving sufficient coverage of the intervention during the study period available and thus impact on target behaviours was limited. Nevertheless, there were a number of positive findings and the Peruvian Ministry of Health has distributed the materials to all regions.

### VITAMIN A AND OTHER MICRONUTRIENTS

Field work for a trial to evaluate the impact of vitamin A supplementation on the response to immunizations in young infants was continued to completion in January 1999 (results available mid-1999). Findings from two completed studies, that explored dietary interventions for improving vitamin A status and strategies for young infant supplementation, were



disseminated in local and national meetings in Ghana, and at international scientific meetings. These findings were part of a review of Ghana's National Vitamin A Programme which recommended distribution of vitamin A supplements during the national (polio) Immunization Days, extension of supplementation to the whole country — but not to children under 6 months of age — use of red palm oil use (RPO) in food aid and supplementary feeding programmes, and trials to promote RPO use in areas where it is more readily available.

Preparations began for two new field trials starting in 1999 in Ghana. The first will evaluate the effectiveness of a newly developed dispensing technology for daily administration of low-dose multiple micronutrient supplements (iron–vitamin A 'Sprinkles'). 'Sprinkles' are particles of ferrous fumarate and retinyl palmitate, micro-encapsulated with a mono- or diglyceride and packed in a single daily sachet dose, for mixing into children's meals. This method of supplementation would avoid some of the problems associated with delivery of iron mixtures and periodic high-dose vitamin A supplementation. If effective, it would be particularly suitable in areas where social marketing of supplements is feasible. The second study will evaluate the impact of vitamin A on maternal mortality, to verify the results from a trial in Nepal, which found a 43% reduction in maternal mortality following weekly vitamin A supplementation of women. It will be a large trial of 103,000 pregnant women, recruited and followed up over four years in three field sites. The trial will clarify the potential role of vitamin A in maternal health programmes, and explain the mechanisms through which its impact might be mediated.

## GHANA HEALTH-SEEKING BEHAVIOUR PROJECT

Timely and appropriate care-seeking for sick children by their families is clearly important for the reduction of childhood morbidity and mortality. In Ghana a study is under way to examine the treatment decisions made by carers, the barriers to appropriate treatment-seeking, and the process and context in which decisions are made. The study uses a newly developed health-seeking behaviour framework that links ethnographic and quantitative findings. The framework focuses on recognition, labelling, patterns of resort and adherence. This project is part of a WHO-funded multi-site study, in collaboration with the Kintampo Health Research Centre, that not only examines care-seeking practices and barriers but also evaluates the feasibility and effectiveness of enhancing care-seeking behaviour for young children.

During the six months of formative research, qualitative and quantitative methods have been used to explore the local illness taxonomy and care-seeking behaviours. Key informants were mothers, healers, druggists and public and private health workers. Problems in illness recognition, labelling, resort to care and adherence were found, and included: a lack of recognition of several danger signs and symptoms, most notably those associated with acute respiratory infections; the classification of several illnesses as 'not for the hospital' resulting in seriously ill children being treated only with traditional medicine; and delayed clinic/hospital attendance due to the use of inappropriate home, healer and druggist medicines. The intervention content has been defined and potential community-based intervention channels identified. The intervention phases of the study are scheduled to start early in the year 2000.

## RESEARCH DEGREE STUDENTS

**Rossana Bojalil** (Mexico). Understanding factors influencing the case management of young children in Hildago, Mexico and their relevance for design of strategies to improve child health and survival.

**Mandi Bruce** (USA). Abortion care in Zambia.

**Juraci Cesar** (Brazil). Community health workers: how can they contribute to the Integrated Childhood Illness Strategy?

**Lisa Davies** (UK). The effect of childbearing patterns, birth spacing and contraceptive use on mortality in Matlab, Bangladesh.

**Paulo Freitas** (Brazil). The epidemic of Caesarean sections in Brazil.

**Tamar Kabakian** (Lebanon). Comparative study of gynaecologic morbidity in 3 countries.

**Najwa Rizkallah** (Palestine). Reproductive morbidity and cardiovascular disease risk factors.

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1999

## MEDICAL STATISTICS UNIT

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<b>Mike Kenward</b> BSc MSc PhD	Professor	<i>Statistician</i>	
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<b>Douglas Altman</b> BSc PhD	Honorary Senior Lecturer	<i>Statistician</i>	
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<b>Tim Clayton</b> MSc	Research Fellow	<i>Statistician</i>	
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The Medical Statistics Unit undertakes a broadly-based research programme in applied projects and in statistical methodology, although these distinctions are not fixed — indeed theoretical work often arises from the applied research, and the results are then used to inform the design and analysis of future studies.

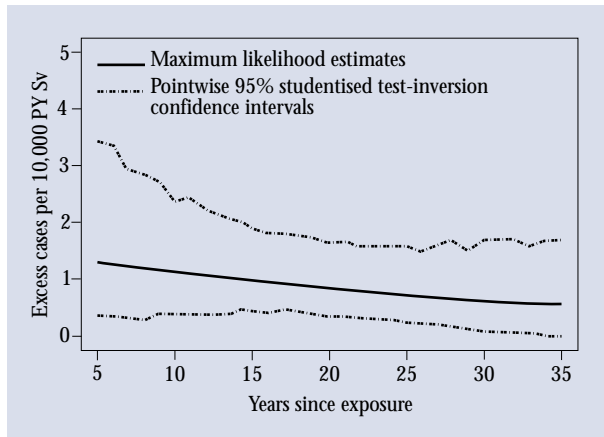
We facilitate research interaction amongst all the School's medical statisticians, and many of our projects involve extensive, often international, research collaborations. In particular, there is an expanding Clinical Trials Group, which is primarily concerned with the planning, co-ordination, statistical analysis and reporting of multicentre clinical trials. The Unit has also established a reputation for being a leading innovative centre for biostatistical methodology relevant to medical research. We also have a broader responsibility for influencing the research development and training of our profession, and held a highly successful research conference in celebration of 30 years of the MSc in Medical Statistics. We

are delighted that Michael Kenward was appointed to the newly-established SmithKline Beecham Chair in Biostatistics.

### METHODOLOGICAL RESEARCH

Treatment differences in clinical trials may be influenced by patient non-compliance, changes of treatment, and the use of rescue medication. We have been actively concerned with devising appropriate methods to incorporate these factors into the statistical analysis in order to achieve more precise effect of treatments, using simulations to compare the biases associated with the different methods. We have also been involved in devising practical model-based methods for handling informative drop-outs in studies investigating predictors of decline in mental health scores in patients with Alzheimer's disease.

Variables in epidemiological studies are often measured with error, and we are considering ways of allowing for simultaneous errors in continuous and categorical data in



*From the Japanese atomic bomb survivors data, it is possible to calculate the expected excess number of cases of particular forms of cancer caused by exposure to a particular dose of radiation (measured in Sieverts). The graph shows the expected number of excess cases of chronic myelogenous leukaemia in females per 10,000 Person-Year Sieverts at risk. The outer lines are 95% pointwise bootstrap confidence intervals.*

multiple regression models. We have developed 'bootstrap' techniques for evaluating parameter uncertainty in statistical models (*see Figure*) and work in this area of computationally-intensive methods was displayed in House of Commons as an example of the best work of young British researchers.

We have continued to work on practical and statistical issues in the conduct of meta-analyses of clinical trials. We have been reviewing and developing statistical models for relating the magnitude of treatment benefit to measured trial level covariates, with appropriate allowance for residual heterogeneity, and have been developing methods to combine the results of trials of different designs.

#### APPLIED RESEARCH

Most members of the Unit work on some aspects of randomized trials. The Unit is currently co-ordinating trials in cardiology, neonatology and hepatology.

The three RITA trials are all involved in the evaluation of treatments for angina. RITA-1 randomized 1011 patients with severe angina to initial coronary angioplasty (PTCA) or bypass surgery (CABG). Although at five-year follow-up there was no difference in risk of death and myocardial infarction between policies, PTCA patients had more re-interventions and recurrent angina, and by a median 6.3 years' follow-up there were similar health care costs in the two groups. In contrast, RITA-2 randomized 1018 patients with moderate to severe angina to policies of immediate PTCA or continued medical treatment. Based on a median 2.7 years' follow-up, early intervention with PTCA was associated with greater symptomatic improvement, but the suggestion of more deaths or myocardial infarctions. Further publications will consider quality of life, economic costs and cost-

effectiveness at up to 3 years' follow-up. The most recent cardiology trial is RITA-3, which is the first large-scale trial designed to test an initial conservative strategy (optimal medical treatment) versus an initial interventional strategy (early coronary arteriography and subsequent PTCA or CABG as indicated) in the management of patients with acute unstable angina. The main outcomes are the rates of death, myocardial infarction and refractory angina. Recruitment began in November 1997, and patients will be followed up at four months, one year and five years.

The TMC trial is comparing two immunosuppressants, and has recruited 606 patients undergoing liver transplantation from all the transplant centres in the UK and Ireland. The primary outcomes are death, retransplantation and treatment failure for immunological reasons, and the one-year follow-up is in progress.

The MRC-funded INNOVO trial is evaluating the addition of nitric oxide to the ventilator gases for newborn babies with severe respiratory failure. Primary outcomes are death and severe disability at one year of age. Nearly 100 babies have been recruited so far from the UK, Ireland, Belgium and Finland.

In addition to trial co-ordination, the Unit acts as the statistical centre for a number of studies such as the international cardiological trials co-ordinated by SOCAR Research in Switzerland. This includes the placebo-controlled ACTION trial of nifedipine in 6000 coronary artery disease patients to be followed for 5 years. We have a varied programme of clinical trial research in asthma, particularly concerning when to start inhaled steroids, whether to use beta-agonists regularly, and the effects of allergen avoidance. We are also statistical collaborators in a trial to assess the effectiveness of a programme to co-ordinate and support follow-up care in general practice after a hospital diagnosis of myocardial infarction or angina pectoris.

A survey of trials centres is under way to ascertain the extent and nature of consumer involvement in research, and qualitative research is exploring the views of trial participants about randomization and other aspects of their experience.

In epidemiology, we are involved in meta-analyses of studies relating plasma homocysteine to risk of stroke and coronary heart disease, and in using meta-analysis to model the relationship between alcohol consumption and death. In addition, we have conducted analyses of the cross-sectional phase of the Marks & Spencer cardiovascular risk factor study, and are involved in the development of the longitudinal phase. Related research is considering methodological aspects of physical activity. Bob Carpenter's cot deaths research has led the European Society for the Study and Prevention of Infant Death to recognize his 'outstanding work in the field of infant mortality'.

**RESEARCH DEGREE STUDENTS**

Christina Bamias (Greece). Methodology of clinical trials.  
François Curtin (Switzerland). Clinical trials methodology.

Mostafa Hosseini (Iran). Analysis of data contained in Iran National Health Survey.

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## PUBLIC HEALTH NUTRITION UNIT

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The Public Health Nutrition Unit has a multidisciplinary research programme of activities primarily concerned with food and nutrition research in the public health context both in developing and developed countries. The Unit's research interests cover areas such as infant, child and adult malnutrition and its management; nutrition and nutritional requirements of adults and of the elderly and their nutritional status assessment in the community; the emergence of non-communicable diseases in developing societies; and nutrition, poverty and social exclusion in the West. Collaborative research is conducted across the School and in partnership with collaborators in other countries.

#### MATERNAL AND CHILD NUTRITION

Promoting good infant feeding practices is crucial for child nutrition both in developing and developed societies. Exclusive breast-feeding of infants for four to six months by mothers needs to be promoted, as breast-milk provides the best food for the first few months of life. Systematic reviews were undertaken on behalf of the Health Education Authority (HEA), UK on the effectiveness of interventions to promote breast-feeding and healthy feeding of infants under one year of age in industrialized societies. The most successful

breast-feeding promotions spanned both pre- and post-natal periods, and involved intensive as well as multiple contacts. Breast-feeding promotions were, however, largely aimed at low income or minority ethnic groups in these developed societies and were successful at increasing initiation of breast-feeding, but few had any impact on the duration or exclusiveness of breast-feeding. In Bangladesh, programmes promoting exclusive breast-feeding are focused mainly on hospitals while the majority of mothers deliver at home. An intervention trial examined the impact of community-based peer counsellors on infant feeding practices, on the duration of exclusive breast-feeding and its impact on infant nutrition. In the intervention group there was early initiation of breast-feeding and significantly more were exclusively breast-fed up to 4 months of age. In this group, 69% of mothers fed their infants colostrum as the first food compared to 11% of the controls, and 70% breast-fed exclusively for 5 months as compared to 6% of the controls. At the end of 5 months, the mean weight-for-length Z score was +0.1 (SD 0.8) in the intervention group and -0.9 (SD 0.8) in the control group. The majority of mothers who breast-fed exclusively, also accepted and practised the lactational amenorrhoea method of contraception. This study demonstrated that trained

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community-based peer counsellors could significantly increase exclusive breast-feeding and appropriate contraceptive practices, with benefits to infant health and nutrition.

Infections are major causes of poor nutritional status of children. *Helicobacter pylori* is a common gastrointestinal infection in children in developing countries which is implicated in poor growth and nutritional status. Studies conducted in urban school children aged 9–10 years in Mexico to assess the prevalence of *H.pylori* infection (using stable isotopic techniques) have indicated prevalence rates of about 48%. The likely risk factors that predispose to *H.pylori* infection in poor households in urban Mexico include overcrowding within a household, the number of children in the house and sharing of beds by siblings. Rural children, particularly girls, in developing countries, undertake arduous work in their homes and outside from an early age. Increased work of this nature is likely to compromise their nutritional status and affect their proper growth. A study of children aged 6–18 years in two villages in rural Nepal showed a significant sex difference in daily workloads; with girls on average, working twice as long as boys (5.8 versus 2.8 hours), spending more time performing heavy work (1.5 versus 0.7 hours). The nutritional status of the girls was no worse than that of the boys thus providing little evidence that the girls' heavy workloads adversely affected their growth in rural Nepal.

#### NUTRITIONAL STATUS OF ADULTS AND THE ELDERLY

The chewing of areca (betel) nut is a common practice in developing countries in Asia among several hundreds of millions of adults – up to 20% of the world's population, principally in South and South-East Asia, East Asia, Melanesia, and in communities of migrants from these regions. Studies in Sarawak, Malaysia have indicated that lower-age related gains in Body Mass Index (BMI) and body fatness and higher resting metabolic rates are seen in chewers of areca nut than in non-chewers. Experimental studies are being conducted in collaboration with partners in Bangalore, India on the effects of areca nut on resting energy expenditure, substrate oxidation, and ratings of hunger.

Studies on assessment of nutritional status of the elderly indicate that the prevalence of malnutrition is similar among the elderly in urban India or rural Malawi. Physical impairment was highest among the elderly in urban India and increased with age and deteriorating nutritional status. Undernutrition is a significant problem among older people even in rural Malawi. These observations highlight the need to incorporate the elderly into nutrition and health programmes in developing societies. The elderly also constitute a proportion of any refugee population. Studies in a Rwandan refugee camp in Tanzania have shown that the prevalence of undernutrition in both sexes was higher among those aged over 60 years as compared to younger adults. Using the National Diet & Nutrition Survey data of the adult population of the UK aged over 65 years, the nature and the extent of under-reporting among the elderly has been

investigated. The level of dietary under-reporting among the free-living elderly was much higher than that observed among the adult population in the UK using a similar methodology. The strongest predictor of low-energy reporting was obesity among elderly men and women, much like that seen among young adults, while social class appeared to be more important than educational status in the elderly in contrast to that seen among adults.

#### CHRONIC DISEASES IN DEVELOPING SOCIETIES

The emerging epidemic of obesity and chronic diseases in developing societies and in those in transition and the risk factors that may be contributing to it, is an area being investigated by the Unit. Studies on obesity among a representative sample of adult women in Kuwait suggest that the prevalence of obesity (BMI > 30.0) was 56% and much higher than that seen in the West. Increasing age and inability to return to pre-pregnancy weight were the two most important independent risk factors. It was also observed that women tended to underestimate their weight with 61% of the participants in the study reporting that their husband's perception of their true weight was also grossly underestimated. Studies are in progress in Pune, India examining the differences in body composition among rural and urban adults who are at increased risk of non-insulin dependant diabetes mellitus and coronary heart disease.

#### URBAN LIVELIHOODS, HEALTH AND NUTRITION

The Unit, in partnership with Proshika (a Bangladeshi social development NGO), continues to explore issues related to vulnerability of livelihoods in Dhaka slums and aims to produce an integrated analysis of the relationship between social, maternal and environmental conditions of households and health and nutritional status of slum dwellers in Dhaka. Analysis related to ill-health on household economy, the coping strategies resorted to by householders to deal with various shocks and stresses as well as the determinants of nutritional status is in progress.

#### FOOD, POVERTY AND SOCIAL EXCLUSION IN THE UK

Work on food, poverty and social exclusion in the UK focuses on three main areas: characterizing problems of nutrition and diet in low-income households; analysis and evaluation of policy responses to these problems; and exploring and evaluating local, community initiatives in this area. Income inequalities influence geographic and economic access to food. Local authority housing and retailing changes have often left poorer estates with a very limited range of food shops, where food is more expensive. Studies with the Institute of Education have been mapping access to healthy food in an ethnically diverse and deprived area. This has involved the construction of indices of price and availability, which can be used with local data to determine levels of physical and economic access to a healthy diet. Participatory appraisal techniques have been used to engage local communities in the research and to lead towards sustainable solutions. Contributions have also been made to efforts at costing a 'minimum living wage' for the UK.



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**Rukhsana Haider** (Bangladesh). Impact of peer counsellors on breast-feeding practices of urban mothers in Dhaka, Bangladesh.

**Ferew Lemma Feyissa** (Ethiopia). Morbidity, immunity and functional status in adults with low Body Mass Index: a prospective study among Ethiopians.

**Francisco Jimenez Guerra** (Mexico). *Helicobacter pylori* infections and growth in pre-school children in Mexico.

**Arete Lagiou** (Greece). Dietary fat and obesity in a Greek adult cohort.

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**Anamaria Ricalde de Freixa** (Brazil). Mid-upper arm circumference in pregnant women and its relation to birthweight and pre-pregnancy weight.

**Miki Yamanaka** (Japan). Children's workload and their growth retardation in rural Nepal.

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Haider R. (Bangladesh) *Impact of peer counsellors on breastfeeding practices in Dhaka, Bangladesh*. (PhD), 1998.

Strawford A. (UK) *The determinants of the lean body mass response to therapy in men with HIV/AIDS related wasting*. (PhD), 1998.



## DEPARTMENT OF INFECTIOUS AND TROPICAL DISEASES

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The Department was created in 1997 in a major reorganization of the management of research and teaching on infectious diseases in the School. The new department comprises all those conducting laboratory-based research, most of the infectious and tropical disease epidemiologists and those involved in clinical research on tropical diseases. The philosophy of the change was to foster synergistic collaboration between these groups to capitalize better on our combined strengths in these disciplinary areas.

An initial stocktaking of strengths and weaknesses identified some key areas where strengthening was required and senior appointments have been made in malaria immunology, bacteriology and clinical tropical medicine. Further such appointments are planned in virology and mathematical modelling. At the same time, an extensive programme of laboratory and office refurbishment is under way associated with moving all departmental staff to occupy the second floor and above of the Keppel Street building.

The breadth of our activities is illustrated in the summaries of ongoing studies and achievements presented by each of the five Units in the pages that follow. The range of work in the Department spans studies aimed at understanding the basic molecular and cell biology of major disease-causing agents

through to applied field and policy research on the disease problems caused by those agents. For some diseases this whole spectrum is covered, specifically this includes the work on malaria and tuberculosis and, to a large extent, trachoma and leishmaniasis. For other diseases our work is focused in a particular area. For example, there is an extensive programme of research on the epidemiology and control of HIV/AIDS, including several large trials investigating behavioural interventions, but we have decided that it would not make strategic sense to try to build up a large programme of laboratory-based research in this area given the strengths of other groups. Rather, we will seek to increase collaborative activity with these groups.

In what has been a very busy and active year on many research fronts, it is difficult to select particular activities to highlight. However, it is appropriate to draw attention to significant developments with respect to our organization of research on malaria. This disease is quintessentially considered as a 'tropical' disease (even though it was not so many years ago a disease endemic in some distinctly non-tropical parts of Europe!) which causes an enormous burden of morbidity and mortality in some of the poorest developing countries, particularly those in sub-Saharan Africa. In recent years the public health impact of the disease has increased due to



changes in its distribution as a result of global climatic changes. In particular, epidemics have occurred in some highland areas previously considered to be areas of low risk for the disease. The spread of chloroquine resistance, the drug around which therapeutic interventions centred for many years, and resistance to other anti-malarial drugs has much worsened the problem. Some significant progress in developing new intervention approaches has been made. New drugs have been developed which may provide temporary respite and the successful development and evaluation of the use of insecticide-impregnated bednets has added a powerful new tool to control efforts. The much-awaited prophylactic vaccines seem tantalisingly close but still elude us.

Global attention to the problem of malaria has been highlighted by changes in the structure of the World Health Organization. In particular, malaria is one of two disease problems selected for special focus and funding (the other is control of diseases caused by tobacco) and the 'Roll Back Malaria' initiative has galvanized international support for making a concerted effort to control the disease, which is responsible for over one million deaths annually, mostly among children in African countries. The School has long enjoyed a high reputation for its work on malaria and this disease has always been a very important component in our tropical disease research portfolio. During the year we were pleased to gain further support for some major activities on malaria in the Department. In particular, a successful bid was made to renew and expand the research programme on the control of the disease funded by the Department for International Development (DFID). We were also successful in gaining renewed support from DFID for our consultancy work on malaria, conducted jointly with the Liverpool School of Tropical Medicine, under the umbrella of the Malaria Consortium. This enables us to provide practical advice and support for those in developing countries responsible for planning and managing malaria control activities at a national and regional level.

The formation of the new department brought many of the key research workers on malaria in the School into the same organizational grouping and one of our major objectives has

been to increase research co-ordination in order to contribute more effectively to global control efforts. A major new initiative has been the formation of a 'Malaria Centre' in the School under the directorship of Brian Greenwood. Through this we are seeking to bring together on a regular basis all of those working on different aspects of malaria in the School, predominantly in the Department, but including major groups in other Departments, such as those working on malaria in pregnancy and on the economic aspects of the disease and its control. At an early stage we appreciated that although our ongoing research on malaria was very broadly based, there was a need for greater interchange and co-operation between different research groups. Further, we realised that our field activities were widely spread and increased focus in particular geographical areas would have considerable advantage in both strengthening ongoing work and in facilitating the planning and organization of new research initiatives. Preliminary visits have been made to several countries in Africa to explore the possibility of setting up a major new collaborative field research activity. We are still at a relatively early stage in this initiative, but the prospects look good for a major development in this area in the coming years. There is much excitement in the Department about the opportunities this will provide for advancing our understanding of the epidemiology and control of the disease.

It is pleasing to report that the excitement in the new Department about malaria research developments is shared with respect to the other major infectious diseases on which we work and, although it is still relatively early days, the 'experiment' of mixing laboratory scientists and epidemiologists is going well!

#### TEACHING AND DIAGNOSTICS GROUP

The teaching and diagnostics group provides research support to students and staff requiring training in diagnostic methods for parasitic and microbial infections. The group is also involved in the development of new diagnostic methods and John Williams has a particular interest in the role of protozoan parasites in irritable bowel disease, collaborating with several clinical groups outside the School on this topic.

1899



1999

## CLINICAL RESEARCH UNIT

<b>David Mabey</b> MA DM FRCP	Professor & Head of Unit	<i>Physician (Infectious Diseases)</i>
<b>Anthony Bryceson</b> BA MD FRCP DTM&H	Professor	<i>Physician (Tropical Medicine)</i>
<b>Brian Greenwood</b> FRS BA CBE MA MB BCh MD DTM&H FRCP FWACP FFPHM	Professor	<i>Clinical Epidemiologist</i>
<b>Kevin de Cock</b> MB BCh FRCP MD DTM&H	Visiting Professor	<i>Physician / Clinical Epidemiologist</i>
<b>Harold Lambert</b> MA MD FRCP FRCPath FFPHM	Visiting Professor	<i>Physician (Infectious Diseases)</i>
<b>Eldryd Parry</b> OBE MD FRCP FWACP	Visiting Professor	<i>Physician (Tropical Medicine)</i>
<b>Keith McAdam</b> MA MB BCh FRCP	Professor <i>(on secondment to MRC Laboratories, The Gambia)</i>	<i>Physician (Infectious Diseases)</i>
<b>Robin Bailey</b> BA MBBS MRCP DTM&H PhD	Senior Lecturer	<i>Physician (Infectious Diseases)</i>
<b>Alison Elliott</b> MD MRCP DTM&H	Senior Lecturer	<i>Ophthalmologist</i>
<b>Allen Foster</b> MBBS FRCS	Senior Lecturer	<i>Physician (Infectious Diseases)</i>
<b>Peter Godfrey-Faussett</b> BA MBBS MRCP DTM&H	Senior Lecturer	<i>Physician/Leprologist</i>
<b>Diana Lockwood</b> BSc MD MRCP	Senior Lecturer	<i>Clinical Epidemiologist</i>
<b>John Porter</b> MBBS MRCP MPH FFPHM FAFPHM DA DCH	Senior Lecturer	<i>Virologist</i>
<b>Kwesi Tsiquaye</b> BSc PhD FRCPath	Senior Lecturer	<i>Physician</i>
<b>Philippe Mayaud</b> MD MSc	Senior Lecturer	<i>(Sexually Transmitted Diseases)</i>
<b>Ron Behrens</b> MD BSc FRCP	Honorary Senior Lecturer	<i>Physician (Travel Medicine)</i>
<b>Peter Chiodini</b> BSc PhD MBBS FRCP	Honorary Senior Lecturer & Clinical Director, HTD	<i>Clinical Parasitologist</i>
<b>Rod J Hay</b> MA BM BCh FRCPath FRCP	Honorary Senior Lecturer	<i>Physician</i>
<b>Paul Kelly</b> MBBS MRCP	Honorary Senior Lecturer	<i>Physician (Gastroenterologist)</i>
<b>Andrew Tomkins</b> MBBS FRCP	Honorary Senior Lecturer	<i>Physician</i>
<b>Stephen Wright</b> BM BS FRCP DCMT	Honorary Senior Lecturer & Consultant at HTD	<i>(Nutrition and Child Health)</i>
<b>Sebastian Lucas</b> BA MA BM BCh FRCP FRCPath	Honorary Senior Lecturer	<i>Physician (Tropical Medicine)</i>
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<b>Andrew Reid</b> MBBS MRCP	Honorary Lecturer	<i>Physician (Infectious Diseases)</i>
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<b>Ali Allouche</b> BSc	Post-Doctoral Research Fellow	<i>Molecular Biologist</i>
<b>David Little</b> BVMS MRCVS	Post-Doctoral Research Fellow	<i>Pathologist</i>
<b>Rachel Baggaley</b> BA MBBS MSc	Honorary Research Fellow	<i>Physician (Community Medicine)</i>
<b>Paul Emerson</b> BSc	Research Assistant	
<b>Wendy Hodsdon</b> BSc	Research Assistant	
<b>Sarah Lewin</b> BA MA	Research Assistant	
<b>Philip Broadbent</b> HND	Technologist	
<b>Tamara Hurst</b> BSc	MLSO 2 Co-ordinator, Wellcome Trust Bloomsbury Centre for Clinical Tropical Medicine	
<b>Claire Bertschinger</b>	Clinical Teacher - Tropical Nursing Course	
<b>Sue Leede</b> RCN	Clinical Teacher - Tropical Nursing Course	
<b>Sarah Henson</b>	Senior Overseas Project Co-ordinator	
<b>Julia Mitchell</b> BSc CertEd	Secretary to Professor Greenwood	
<b>Vivienne Hammer</b>	Secretary to Allen Foster	
<b>Annastella Costella</b>	Unit Secretary	

## FUNDING BODIES

Ciba-Geigy Ltd

Commission of the European Communities

Department for International Development (DFID)

Edna McConnell Clark Foundation

GlaxoWellcome plc

Hospital and Homes of St Giles

LEPRA

Medical Research Council

National Institutes of Health (US)

Rockefeller Foundation

The Wellcome Trust



The research programme of the Unit encompasses infectious diseases of major public health importance in developing countries. Activities include trials of new therapies, vaccines and educational interventions; the development of new diagnostic tests; studies to elucidate the immunological and molecular correlates of pathogenesis and protective immunity, and to identify genetic polymorphisms conferring protection or susceptibility to infectious diseases; health services research which aims to identify the most efficient and cost-effective way to deliver health care; and health policy analysis.

Many members of the Unit are practising clinicians, but many are also trained in epidemiology and/or laboratory science. We collaborate widely with colleagues in other Units and Departments within and outside the School, and our research covers many disciplines, from molecular immunology to public health and policy. Members of the Unit have initiated and are responsible for major research programmes in Zambia, Tanzania, The Gambia, Uganda, South Africa and India, and are also closely involved with clinical research and teaching at the Hospital for Tropical Diseases, London. The Wellcome Trust Bloomsbury Centre for Clinical Tropical Medicine is based in the Unit.

## TUBERCULOSIS

Several projects focus on the interaction between *Mycobacterium tuberculosis* and HIV. In collaboration with the Uganda Virus Research Institute in Entebbe, the relationship between cellular immune responses and progression to active tuberculosis is being investigated in a cohort of 700 HIV-positive individuals. At baseline, associations were observed with intestinal nematode infestation. Individuals with intestinal nematodes had reduced interferon-gamma responses to *M. tuberculosis* antigens, suggesting that worms may reduce immunity to tuberculosis. Unexpectedly, it was also found that individuals with a BCG scar were less likely to have intestinal nematodes than those without, and this was not a confounding effect of socioeconomic status. This raises the fascinating possibility that BCG immunization in childhood may have a long-term effect on the type 1/ type 2 balance of the immune system influencing susceptibility to helminths.

Two studies, in different towns in South Africa, have been investigating the reasons behind the exceptionally high incidence of mycobacterial disease in South African gold miners. DNA fingerprinting of all isolates from a prospective cohort has demonstrated that there is intense ongoing transmission of TB, despite a well-resourced control programme that is curing 88% of new cases. The increasing TB incidence appears to be due to the introduction of HIV infection, now at high prevalence, into a population which is already predisposed to TB because of occupational exposure to silica dust. The effects of HIV infection and silicosis on TB incidence were shown to combine in a multiplicative fashion, explaining why TB incidence remains highly dependent on silica exposure and silicosis in HIV-positive miners. TB

incidence among HIV-positive miners has increased 4-fold in the period 1991 to 1998, suggesting either more advanced immunosuppression or increasing TB transmission within the workforce, or a combination of the two. The failure of the well-run TB control programme, which includes all the features of the recommended WHO DOTS strategy plus an active case-finding component, to contain the current HIV-associated TB epidemic suggests that a more radical approach may be required to achieve short-term control, although improved dust control and HIV prevention have to be the long-term goals. Possibilities would include more active case finding with, for example, sputum screening, or mass preventive therapy.

Action-oriented operational research in urban Lusaka has emphasized the drop out at every stage of the diagnostic process for people with a cough and is currently exploring the role of non-governmental organizations in supporting TB control. A randomized trial of 24 vs. 6 months of isoniazid as tuberculosis preventive therapy in people living with HIV has recently started, and a pilot site is being developed in Lusaka that uses voluntary counselling and HIV testing as an entry into a more holistic package of care for TB and other HIV-related illnesses.

## DFID TUBERCULOSIS RESEARCH PROGRAMME

The DFID Tuberculosis Research Programme links the School with the Nuffield Institute for Health in Leeds and addresses four areas: the development of new knowledge about how to prevent and treat TB effectively in developing countries; the development of new and improved techniques to diagnose TB and drug resistance; improved understanding of the options for the effective delivery of TB interventions through health care systems; and the development of effective mechanisms for capacity building in developing countries through collaboration and training.

Major themes of the programme include: preventive therapy in persons with HIV infection, the development of new, affordable diagnostics tests, the introduction and critique of the international TB control strategy of directly observed therapy short course (DOTS), and the interaction between TB patients and different health care providers in the public and private sectors. The work is concentrated in several countries including: Zambia, Kenya, Malaŵi, South Africa, India, Pakistan and Nepal. The programme works through the development of collaborative links with academic, research, non-governmental, and government organizations in these countries.

During the past year, new work has begun in South Africa with the TB Association of the Western Cape to develop a community-based TB/HIV care model. In Malaŵi, work continues on TB transmission, risk factors, presentation delay and glandular TB. Following the review of a LEPROA-funded pilot TB/leprosy integration project among tribal communities in Orissa, India, in 1998, there is now the

opportunity for further qualitative research on the integration of TB services into the state primary health care infrastructure. Work supported by the DFID and Cooperation Française has led to the development of a research project to look at the perceptions and beliefs of communities about TB in several West African countries. In the laboratory, further work is being conducted on the mycobacteriophage replication technology developed for diagnosis and drug susceptibility testing.

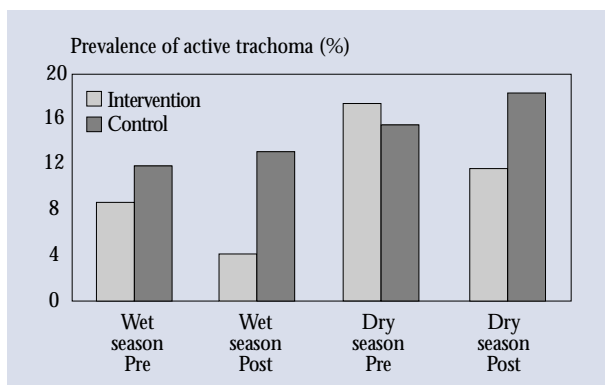
### MALARIA

During 1998, a further evaluation of the circumsporozoite malaria vaccine RTS,S developed by SmithKline Beecham and the Walter Reed Army Institute of Medical Research was undertaken in The Gambia. Approximately 300 adults were vaccinated with 3 doses of RTS,S or with rabies vaccine and followed throughout the 1998 malaria transmission season. Clinical and parasitological data collected during the surveillance period have now been collated and typing of malaria parasites collected from study subjects has been completed at the School. The vaccine code will be broken in June 1999.

### TRACHOMA

Research on blinding diseases in developing countries has been greatly strengthened by the recruitment of Allen Foster from the International Centre for Eye Health. His current work includes the outcome of different techniques for cataract surgery, the causes and control of childhood visual loss and blindness and the control of ocular infections particularly due to trachoma and onchocerciasis. Trachoma is a particular interest of the Unit, and two important trials were completed in 1998: a trial of community-based mass treatment with the new azalide antibiotic azithromycin, and a trial of fly control, using ultra low volume spraying with deltamethrin. Mass treatment was shown to be well accepted, and to reduce the village-wide prevalence of active trachoma for at least 12 months. Fly control reduced the prevalence by 60% over a 3-month period (*Figure 1*).

The complete genome sequence of *Chlamydia trachomatis*, the cause of trachoma, was published in 1998, revealing a number of new potential determinants of pathogenesis and



*Figure 1. Prevalence of active trachoma before and after fly control.*

immunity. Four new putative outer membrane proteins have been cloned and expressed, and their immunogenicity is being explored, using a panel of sera from clinically well characterized individuals from trachoma-endemic populations in The Gambia.

### ACUTE RESPIRATORY INFECTIONS

Preparations continue for a large efficacy trial of a new nine-valent pneumococcal conjugate vaccine in Gambian infants. A phase 2 trial involving 600 infants was started at the beginning of the year and is nearing completion. This has been undertaken to check that administration of the new conjugate vaccine does not interfere with responses to routine EPI vaccines. Pilot testing of many of the procedures that will be used in the trial has started and it is anticipated that vaccination of the 30,000 infants in the main trial will commence around the end of 1999. The trial will last approximately five years.

### ENTERIC PROTOZOAL INFECTIONS

A 3-year longitudinal study of transmission of enteropathogens in Misisi, an unplanned settlement in Lusaka, Zambia, has recently started. High transmission rates had been previously found in this community. A cohort of adults is being followed, with systematic evaluation of episodes of illness, in which the presence of enteric infections is related to the severity of tropical enteropathy evaluated by jejunal biopsies and permeability studies. Initial surveys and investigations suggest a high burden of morbidity, both infectious and non-infectious. Preliminary assessment of the jejunal biopsies indicates that the small intestinal morphological change associated with living in the tropics is indeed present, but full evaluation of structure, function, and defence molecule expression is only just beginning.

### LEPROSY

The strong collaboration with Dhoolpet Leprosy Research Centre, Hyderabad continues and several new projects have been established there in the past year. The main focus continues to be the role of cytokines in causing tissue damage since the identification of cytokines associated with pathology may pave the way for new treatments. A series of nerve biopsies was collected from patients with acute neuritis and the cells and cytokines in acutely inflamed nerves were identified by immuno-histochemistry. CD4 cells predominate in nerve from patients with borderline forms of disease. Patients with borderline tuberculoid and borderline lepromatous leprosy have abundant intra-neural interferon gamma. This cytokine is pro-inflammatory and is probably activating other cells to cause damage. In contrast nerves from patients with lepromatous leprosy, although they have clinical evidence of neuritis, have almost no interferon gamma. Steroid treatment reduces the CD4 cell infiltrate in skin granulomata during reversal reactions, and results in a marked reduction in the local production of interferon gamma. Abundant chemokine production was found in skin lesions across the leprosy spectrum, even in anergic



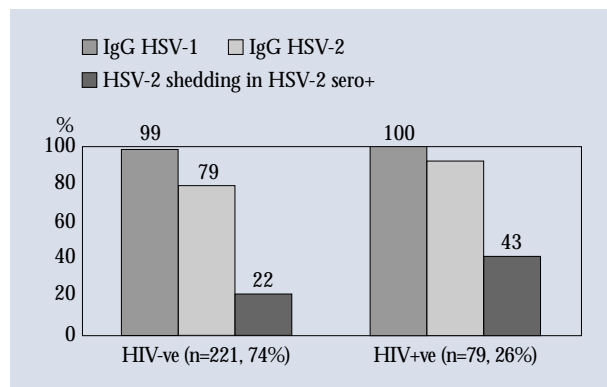
lepromatous patients. Thus the anergy seen in lepromatous lesions may be occurring as a local phenomenon.

#### DFID WORK PROGRAMME ON HIV/AIDS AND STDs

The relationship between HIV transmission and other sexually transmitted diseases (STDs) is a particular interest of the Unit. A previous study, conducted in collaboration with colleagues in the Infectious Disease Epidemiology Unit (IDEU) and in Mwanza, Tanzania, found that improved treatment of bacterial STDs can reduce HIV incidence. However, viral STDs, especially *Herpes simplex* type 2 (HSV 2) are an increasing problem in countries with advanced

HIV/AIDS epidemics; in rural Tanzania, it was found that almost 50% of girls were infected by the age of 20 years. In the Central African Republic, a study conducted in collaboration with colleagues in Paris and Bangui showed that HIV-1 infection increased the shedding of HSV 2 in the female genital tract (*Figure 2*), implying a degree of 'epidemiological synergy' between the two infections.

WHO estimates that 50% of new HIV infections are acquired by people aged less than 25 years, making prevention in this age group the top priority. A community-randomized trial is being undertaken, in collaboration with colleagues in Tanzania and in IDEU, of a behavioural intervention, supported by more 'adolescent friendly' STD treatment services, against HIV and other STDs in Tanzania.



*Figure 2. HSV-1&2 antibody sero-prevalence and HSV-2 shedding by HIV serostatus, amongst 300 women attending a multipurpose reproductive health clinic in Bangui, Central African Republic. (Source: Mbopi-Keou et al (unpublished, 1999)).*

Syndromic management for STDs has been strongly promoted by the WHO, especially since the publication of the original Mwanza trial showing that it could reduce HIV incidence. However, it is difficult to apply in women, and a study among rural women in Bangladesh found that in this conservative society, with a low STD prevalence, it was not a cost-effective control strategy; it would be better to target services to higher risk groups, or to men. Screening of pregnant women for syphilis was found to be cost-effective even with a prevalence of less than 1%. Preliminary results of a trial in Mwanza suggest that a single dose of intramuscular benzathine penicillin is sufficient to prevent adverse pregnancy outcomes due to syphilis.

#### RESEARCH DEGREE STUDENTS

**Willie Abela Githui** (Kenya). Drug resistance of TB: epidemiology in Kenya.

**Habib Najibullah Ayub** (Afghanistan). Health survey in holiday travellers.

**Anna-Karin Hurtig** (Sweden). TB in Nepal.

**Alice Amanda Kirkaldy** (UK). Chemokines in reversal health in leprosy.

**Monique Oliff** (South Africa). Analysis of integrated STD care in reproductive health services in Tanzania.

**Emilia Jesus Encarnacao Valadas** (Portugal). Immunology of TB.

**David G Withum** (USA). HIV epidemiology.

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PORTER JDH. (UK) *Tuberculosis in the 1990s and the role of preventive therapy in low income countries* (MD), 1998.

TEMPERTON NJ. (UK) *Functional studies on superoxide dismutase in Trypanosoma cruzi*. (PhD), 1998.

WEST B. (UK) *Neisseria gonorrhoeae isolated from population groups in the Lake Zone, Northern Tanzania*. (PhD), 1998.

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## DISEASE CONTROL AND VECTOR BIOLOGY UNIT

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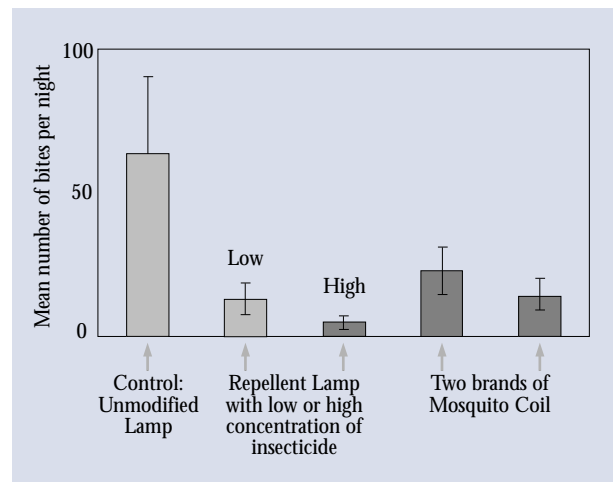
## MALARIA AND ITS VECTORS

Unit staff, with their Tanzanian colleagues, have been surveying the prevalence of malaria fever, anaemia and splenomegaly in children in relation to entomological inoculation rate (EIR) in a lowland area near Muheza and a highland area near Amani at about 1200 metres. Results confirm and amplify those of the late Ruth Ellman that in the highlands, where the EIR is about 5% of that in the lowlands, all the measures of mild and chronic malaria morbidity are also lower. In both areas the prevalence of malaria infection and morbidity decline steeply with age between 1 and 6 years. These data do not support the point of view that converting an area of high malaria transmission to one of moderate transmission (e.g. by use of treated bednets) would delay occurrence of malaria morbidity until a later age and could in the long run make the overall problem worse. Surveys of villages where treated nets have been in use for 2 or 3 years show that prevalence of anaemia and splenomegaly are markedly less than in similar villages without nets.

Continuing the Unit's work on low-cost technology for vector control in the community, a new method has been devised for the application of insecticide as a nocturnal domestic mosquito repellent. This uses a modified version of the hand-made kerosene lamps which in many African communities are the most common source of light at night. The kerosene is used to heat a small amount of cooking oil, containing a trace of transfluthrin, a volatile pyrethroid. This has been found to reduce indoor mosquito biting rates by over 90%, better than common brands of mosquito coil (*see Figure*), and at far lower cost; the insecticide for one evening's use costs less than half a US cent.

Meanwhile, the Unit's work on the dip-it-yourself approach to the promotion of impregnated mosquito nets, reported in the *Research Report 1995-6* has become increasingly

influential. Now all four of the major manufacturers of pyrethroids have launched, or are preparing to launch their own products in this form. The Technical Support Network on Insecticide-Treated Nets of the Roll Back Malaria Programme now agrees on the importance of the dip-it-yourself approach in Africa.



*In a suburb of Dar es Salaam, five teams of mosquito catchers sat from 6pm to 10pm every night for 25 nights, counting the mosquitoes biting them. The repellent lamp (with different concentrations of insecticide) was compared with two brands of mosquito coil and with the control (an unmodified lamp).*

Another research project has sought to test winter spraying as a strategy for control of the malaria vector *Anopheles arabiensis* in KwaZulu, South Africa. In the dry winter season, populations of *An.gambiae* sl. appear to retreat to a few widely scattered permanent water holes, whereas in the rains they are everywhere. It has long been speculated that insecticide treatment of these small and clearly defined winter foci could prevent the normal rainy season expansion. Microsatellite

population genetic analysis was used to determine whether the summer population expansion originated locally from the small numbers of surviving resident mosquitoes rather than from migrant mosquitoes moving into the region from more seasonally stable populations elsewhere. The results provide evidence of limited migration within the region, supporting field trials of dry season larviciding. These are now under way, and the impact of this intervention upon the local incidence of malarial disease is being monitored. Microsatellite markers will be used to measure the impact upon local genetic diversity in the vector population.

In Hubei Province, China, comparison of deltamethrin-treated mosquito nets and DDT residual wall spraying showed that both methods were equally effective in the control of malaria but, as the treatment of nets was cheaper and preferred by the population, this was selected as the method of choice.

#### DFID MALARIA PROGRAMME

This year saw the completion of the last full year of the current DFID malaria programme, its favourable review by DFID, and also the preparation of a new 5-year programme on the applied aspects of malaria and its control, which was selected by DFID and funded. It has also been a year of unprecedented activity in malaria as a whole, as the subject rises to the top of WHO's agenda for the first time since the 1970s and School staff have been much involved in the preparation for Roll Back Malaria.

Several major projects have come to fruition: detailed analysis of the results of our large community-randomized trial of insecticide-treated mosquito nets (ITMN) show them to be comparable with, and even to exceed, wallspraying against *Anopheles culicifacies*-transmitted malaria in rural Gujarat, India. The overall approach to national programmes has taken shape; a global review of existing programmes, carried out in the field with the Malaria Consortium, has been completed as a guide to operational work on a larger scale; and work is under way on an innovative alternative approach to preventing biting by vectors. Vaccine trials completed have indicated no breakthroughs as yet, but molecular methodology has been used to detect strain pattern modification by vaccines and to separate reinfections from recrudescences in drug trials. The first phase of the African highland malaria project was completed and initial plans for a network for forecasting malaria epidemics in highland areas have been drawn up with Control Programmes in Kenya, Uganda and Tanzania. The predictive use of the El Niño phenomenon in epidemic forecasting developed: in India, Gujarat State proposed a major initiative in this area based upon DFID programme work. The urban malaria studies in Surat are now yielding results relevant to improved service delivery and prevention.

#### LEISHMANIASIS

The changing epidemiology of American cutaneous

leishmaniasis (ACL) and its significance for control policy remains the principal focus of research. In most endemic countries, a steadily increasing health burden from ACL is suggested by the number of cases reported annually by health services since the 1980s. This pattern was confirmed in Brazil by an analysis of active search data (clinical and immunological) collected from a prospective survey in Pernambuco, indicating a 10-fold increase during the last 10 years. This region typifies the new epidemiology of ACL as transmission by sandfly vectors (in this case *Lutzomyia whitmani*) is largely in the domestic environment. Where ACL transmission is domestic, vector control becomes a feasible intervention; but the decision where to target the limited resources available for ACL control requires reliable spatial data on the risk of infection. Widespread monitoring of sandfly abundance is not a realistic option, so that distributional maps generated by risk factor analysis are paramount. In the coffee-growing region of Huila Department, Colombia, a regression analysis of newly collected sandfly data demonstrated that 81% of the spatial variance in abundance of *Lu. longiflora* (the suspected ACL vector in this region) can be explained by variation in rainfall, temperature, altitude and habitat type. Domestic transmission was again indicated, especially where houses were close to traditional coffee plantations, a preferred habitat for this sandfly species.

Domestic transmission of ACL depends on the behavioural traits of the local sandfly vectors and on the abundance of potential domestic reservoir hosts. Field studies on the host-seeking behaviour of sandflies (*Lu. whitmani*) have provided the first evidence of consistent behavioural heterogeneities within sandfly populations: sandflies were significantly more likely to seek one host type (either cattle or horses) if they had previously tried to feed from the same host. However, population genetic studies of sandfly populations (in collaboration with the Natural History Museum), using three newly discovered microsatellite loci, failed to find any strong evidence for population structure amongst *Lu. whitmani* sandflies collected over a radius of 15 miles (including both domestic and forest populations), and so the possibility that differences in host preference may be learnt rather than genetically determined cannot be discounted. The odour cues that attract sandflies to particular hosts are not known, but field studies (in collaboration with Universidade Federal do Paraná) comparing the attractance of human hosts with the attractance of equivalent emissions of carbon dioxide (to *Lu. whitmani* and *Lu. intermedia*) are the first to demonstrate that the relative attractance of hosts in the field is not solely due to differences in carbon dioxide output, i.e. there must be additional specific host odour cues.

Studies on domestic reservoir hosts (in collaboration with the University of Cambridge) are concentrating on dogs, as these have a suspected role in the domestic transmission of ACL throughout much of its range. For the first time, ACL prevalence in dogs has been measured by a PCR-based assay



on blood, rather than by the less-specific serological assays or the less-sensitive parasitological diagnoses previously used. The assay identified *Leishmania (Viannia)* DNA in the blood or bone marrow of 8.1% of dogs sampled in Huanuco Department, Peru (an endemic region of *Le. braziliensis* and *Le. peruviana*). This not only provides evidence of a relatively high ACL prevalence amongst this ubiquitous domestic animal, but also suggests that infected dogs are likely to be infectious to bloodfeeding sandflies.

### FILARIASIS

A rapid epidemiological assessment method using prevalence of hydrocele was found to provide a good monitoring indicator of the night blood microfilariae rate in Ghana. This can be used effectively by peripheral health workers, following questioning of community key informants. The method will be used as the basis for discovering pockets of endemicity in the initial phase of a country-wide control programme.

### ENVIRONMENTAL HEALTH

The programme of research into domestic hygiene behaviour continues. Manuals on how to carry out formative research for hygiene promotion, based on previous research in the Unit, have been distributed world-wide by UNICEF and other agencies. An evaluation of an experimental hygiene promotion programme carried out in Burkina Faso showed that handwashing with soap after contact with children's stools had increased from 13% to 31% as a result of the intervention. With the support of Unilever Research, a multidisciplinary model of the motivation for hygienic behaviour has been developed which includes psychological and cultural factors such as the desire to order and classify, to beautify, to display and to avoid objects that elicit disgust. Environmental and habit-related factors were also found to be important as determinants of hygiene practices in field work in the Netherlands and in India. The findings suggest that hygiene is not just a simple matter of germ avoidance and that other motivations for hygiene are important if practices are to improve. The cross-disciplinary work continues in current projects to promote safe domestic hygiene in Europe and Africa.

Studies have continued on the control of atopic allergies through interventions to control house dust mite allergen. A wide range of domestic vacuum cleaners advertised as 'allergen friendly' are being tested using a specially developed series of rigorously controlled experiments to measure allergen removal, dispersal and retention. The first full-scale clinical trials utilizing the impregnated mattress covers developed by Unit staff to control mite allergens are ready to begin in spring 1999 in collaboration with the Department of Thoracic Medicine at The Royal Free Hospital, London. Collaboration has begun with several regional health authorities to monitor the development and distribution of insecticide resistance in the UK head louse population. Early results indicate widespread resistance to all classes of pesticides currently in use, organophosphates, carbamates and even the most recently introduced pyrethroids.

Frequent flooding in the slums of developing countries is a potentially serious problem in environmental health, as flood waters are heavily polluted by overflowing sewers and latrines. Analysis was completed on a study of drainage and flooding in Indore (India). Major results included the finding that small changes in road design could substantially reduce the frequency and extent of flooding, even in 'upgraded' slums where drainage had already been improved. The work points to the importance of the careful design of road systems as drainage networks. Such an approach would not only cost less than pipes or channels, but would also be less susceptible to blockage from rubbish and construction debris. The study has also yielded a manual on drainage evaluation for practitioners.

A sero-epidemiological study (IgA) of calicivirus-Mx in the general population, studying both seropositivity and seroresponse, was concluded in Mexico. Hygiene variables (cleanliness of mother's clothes, handwashing, direct contact with partially treated wastewater and with dogs) appear as important risk factors for an infection previously only studied in outbreak conditions, and generally associated with contaminated drinking water supplies, with oysters, or with illness among food handlers.

### RESEARCH DEGREE STUDENTS

**Hussain Al Samt** (United Arab Emirates). Epidemiology of group A streptococci (*Streptococcus pyogenes*) in Dubai, United Arab Emirates.

**Morten Holst Andreassen** (Denmark). Genetic sex separation systems in *Anopheles* with special emphasis on the use of the sterile insect technique.

**Christopher Day** (UK). Risk assessment in food hygiene and food-borne hygiene.

**Martinho Dgedge** (Mozambique). Implementation of insecticide treated net programme for malaria control in Mozambique through the primary health care system: socio-economic factors associated with equity and sustainability.

**Abdoulaye Diarra** (Mali). A critical study of the integration and implementation of malaria and schistosomiasis national control programmes in Mali's decentralized health system.

**Iwan Dwiprahasto** (Indonesia). Epidemiology of malaria during pregnancy in Indonesia.

**Wanjiku Kamau** (Kenya). Health of displaced and transient populations.

**Jan Kolaczinski** (Germany). Aspects of pyrethroid resistance in relation to impregnated bednets.

**Katrin Gaardbo Kuhn** (Denmark). The potential effect of global warming on the distribution and transmission of malaria and leishmaniasis in Europe.

**Dapeng Luo** (China). Spatial prediction of malaria in the Red River Basin, Yunnan, China, using geographical information systems and remote sensing.

**Edward Magbity** (Sierra Leone). Entomological and other techniques for the evaluation of pyrethroid treated nets.

**Magda Magris Crestini** (Venezuela). The efficacy of treated nets in Yanomami communities in the Upper Orinoco region of Venezuela.

**Shyam Misra** (India). Indoor residual spray versus treated mosquito nets using deltamethrin to control malaria: a community randomized trial in rural Surat, India.

**Jamalun Nessa** (Bangladesh). Epidemiology of *Helicobacter pylori* in Bangladesh.

**Lyda Osorio** (Colombia). Antimalarial drug resistance in the border Amazon region of Colombia, Brazil and Peru: assessment of its determinants of emergence and spread.

**Sophal Oum** (Cambodia). Community based health surveillance in rural Cambodia

**Raul Pardo Puentes** (Colombia). The ecology and control of cutaneous leishmaniasis vectors in Huila Department, Colombia.

**Aree Pethleart** (Thailand). Importance of asymptomatic malaria and its infectivity to *Anopheles* mosquitoes in Mae Hong Son Province, Thailand.

**Richard Reithinger** (Germany). The evaluation of dog control for reducing the risk of human cutaneous and mucocutaneous leishmaniasis.

**Jorge Ricardez Esquinca** (Mexico). Assessing the impact of ivermectin on onchocerciasis in Chiapas State, Mexico.

**Claudia ME Romero-Vivas** (Colombia). Studies on *Aedes aegypti* and dengue virus transmission in an urban area of Central Colombia: biology, surveillance and control interventions.

**Mayira Sojo-Milano** (Venezuela). Epidemiological characterization of malaria foci in Venezuela: a comprehensive approach to malaria, poverty and population mobility in the state of Sucre.

**Sarai Vivas Martinez** (Venezuela). Epidemiological mapping of the onchocerciasis focus in Amazonas State, Venezuela.

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## ELECTRON MICROSCOPY AND HISTOPATHOLOGY SERVICES

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**Aden C Smith** MSc

Reader and Head of Unit  
 Honorary Senior Research Fellow  
 Technologist  
 Technologist  
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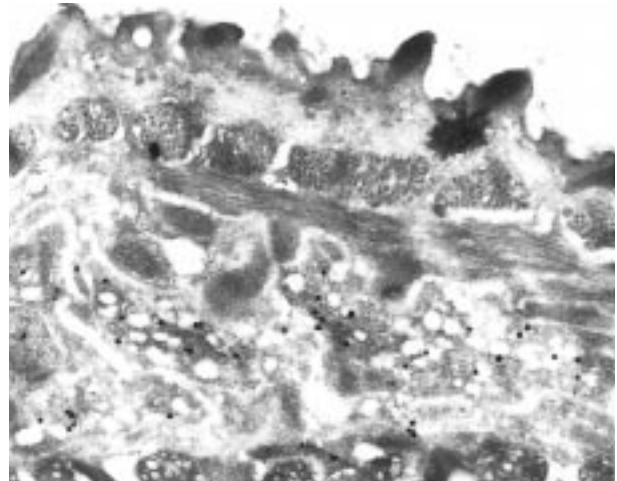
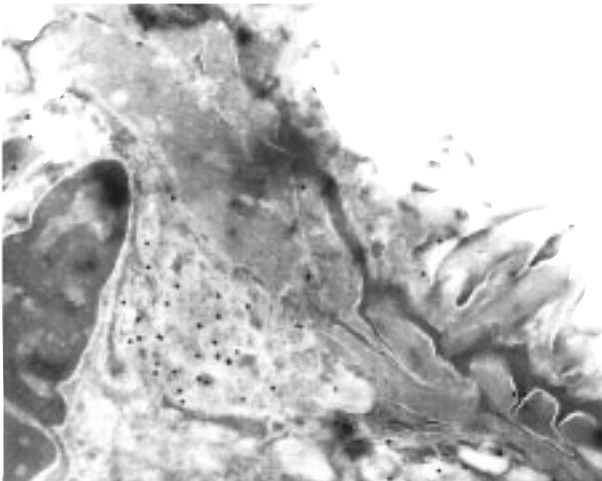
*Parasitologist*  
*Microbiologist*

### FUNDING BODIES

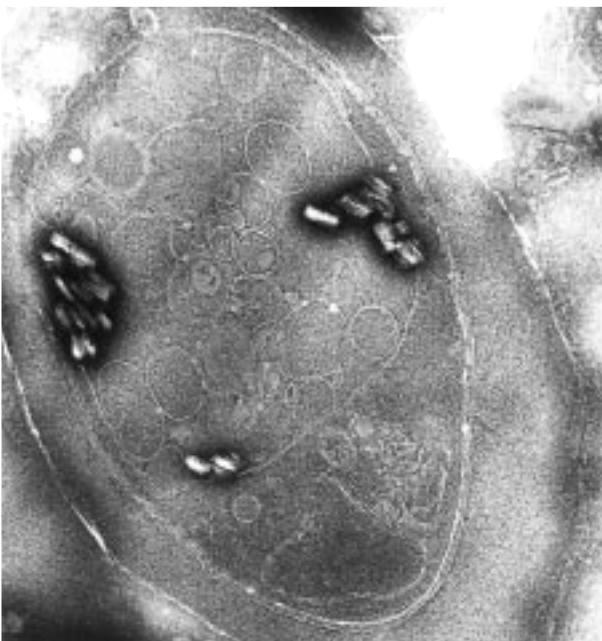
CBD Porton Down  
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Techniques appropriate for research in the School continue to be developed. Cryo-electron microscopy allows the examination of specimens that have been deep frozen with only mild chemical fixation and no subsequent dehydration and embedding in resins. This approach enables better preservation of antigens and more sensitive immunocytochemistry. It produces a very different image of the

ultrastructure of cells and tissues (see Figures contrasting traditional transmission electron microscopical with cryo-electron microscopical images of the erythrocytic stages of *Plasmodium falciparum* and the tegument of *Schistosoma mansoni*). Cryo-EM is currently being used for the localization of myosin specific antibodies in *Schistosoma japonicum* (with Yaobi Zhang, Immunology Unit); surface



Micrographs of *S.mansoni* following cryo-preservation (left) and routine fixation (right).



Micrographs of *P.falciparum* erythrocytic stage following cryo-preservation (left) and routine fixation and embedding (right).



proteins on *Chlamydia* EBs (with Ru-ching Hsia, Pathogen Molecular Biology and Biochemistry Unit (PMBBU)) and other antigens on *Caenorhabditis elegans* (with George Joshua, Immunology Unit); *Trypanosoma cruzi* (with Shane Wilkinson, PMBBU); and *Entamoeba histolytica* (with Jorge Tovar, PMBBU).

In a project with Dr Y Miao and Professor B Gazzard

(Chelsea and Westminster Hospital, London) gut biopsies are being examined both before and after triple therapy. The focus of the study is on gut pathogens, in particular Microsporidia and *Cryptosporidium*, and changes in pathology. A collaboration on the function of the Golgi network and rab proteins in *Trypanosoma brucei* has continued (with Drs H and M Field, Imperial College of Science, Technology & Medicine).

#### PUBLICATIONS

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1899



1999

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Professor &amp; Head of Unit

Professor

Professor

Professor

Professor

Reader

Reader

Reader

Senior Lecturer

Immunoparasitologist

Senior Lecturer

Senior Lecturer

Honorary Senior Lecturer

Honorary Senior Lecturer

Honorary Senior Lecturer

Lecturer

Lecturer

Honorary Lecturer

Honorary Senior Research

Fellow

Research Fellow

Research Fellow

Research Fellow

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*Immunologist**Immunologist**Immunologist**Immunoparasitologist**Immunoparasitologist**Immunologist**Parasitologist**Immunologist**Biochemist**Clinical Immunopathologist**Viral Oncologist**Molecular Virologist**Dermatologist**Molecular Virologist**Parasite Biochemist**Immunologist**Microbiologist**Immunologist**Immunologist**Immunologist**Immunologist**Immunologist**Immunologist**Immunologist**Molecular Biologist**Immunologist**Immunologist**Immunologist**Immunologist**Immunoparasitologist**Immunologist**Immunologist**Clinical Immunoparasitologist**Immunologist**Immunologist**Immunologist**Immunologist**Molecular Biologist**Immunologist**Immunologist**Parasitologist***FUNDING BODIES**

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The Immunology Unit continues its traditional blend of research into basic mechanisms of host immunity, involvement in the evaluation and monitoring of immunity at the population level, and the transfer of immunological interventions to the field. Added impetus to the experimental work of the Unit has come over the past 2 years with the acquisition of new equipment for cell biology, the appointment of new staff and the completion of new laboratory space.

## INFLAMMATION AND MECHANISMS OF HOST RESPONSE

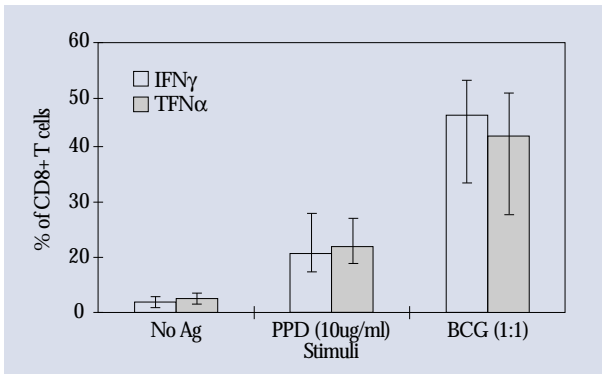
Studies on the host response to *Burkholderia pseudomallei* the causative agent of melioidosis, continue to progress rapidly. Pitak Santanirand has shown that the organism is only able to induce a strong TNF $\alpha$  response from macrophages when they have been IFN $\gamma$  stimulated. However, in contrast to most other gram negative bacteria, the lipopolysaccharide of *B.pseudomallei* does not appear responsible for TNF $\alpha$  triggering. Working in Greg Bancroft's laboratory, Ganjana Lertmemongkolchai has shown that neutralization of IFN $\gamma$  *in vivo* in an experimental model of infection increased the susceptibility by 100,000 fold. We have now demonstrated that *in vitro* incubation of *B.pseudomallei* with naive leukocytes stimulate the rapid production of IFN $\gamma$  by NK cells and CD8, but not CD4 T cells. This early IFN $\gamma$  response is dependent on two key cytokines, IL-12 and IL-18. We believe this mechanism of NK cell and bystander CD8 T cell activation is also an important component of the innate immunity to other intracellular pathogens.

Silvia Bino and colleagues at Imperial College of Science, Technology & Medicine are continuing their investigations of antisense peptide regulation of interleukin 1 $\beta$ . An inhibitory peptide was discovered to share amino acids with the IL-1 $\beta$ R binding site, adding another twist to this exciting

new line of research. Kikki Bodman-Smith, with colleagues in Glasgow, has demonstrated that the C-reactive protein (CRP) has a very strong binding affinity for the Fc $\gamma$ R1 receptor present on macrophages and activated neutrophils. This finding should have important implications for the biology of pathogens which directly or indirectly bind CRP.

Work by David Meyer has discovered the first cytokine-like molecules from parasitic nematodes, macrophage migration inhibition factor (MIF) orthologues of *Trichinella spiralis*, *Trichuris muris* and *Brugia pahangi*, as well as the first sub-micromolar ligand for human MIF, namely haematin.

Hazel Dockrell's research group are investigating T cell and macrophage responses to pathogenic mycobacteria and their antigens, in order to develop tests which would be reliable correlates of protective immunity. Recombinant vaccinia viruses, expressing individual mycobacterial antigens, produced by Adam Malin, were used to show that BCG-stimulated CD8 T cells recognized antigens including the Ag85A, 85B, 19kDa and 38kDa antigens. Current work involves mapping the peptide epitopes recognized within the Ag85A antigen using synthetic peptides and ELISPOT assays for cytokine production. Hazel Dockrell also co-ordinates an EC-funded collaborative study with partners in Birmingham, Oxford, Lisbon, The Gambia and Mexico. The new phase of this study, which combines groups working on both tuberculosis and leprosy, is investigating the activation of CD8 and  $\gamma\delta$  cells, and the role of a novel pathway of mycobacterial killing mediated by the P2z receptor. The P2z work, led by Dr D Kumararatne and Dr DA Lammis at the University of Birmingham, is of great interest as not only does ATP-mediated cytotoxicity for infected macrophages kill the intracellular mycobacteria, something human cells find it hard to do, but there is evidence for heterogeneity among healthy subjects in their expression of the P2z receptors.



*CD8+ T cells make IFN $\gamma$  and TNF $\alpha$  in response to mycobacterial antigens. This response is greatest to stimulation with a live *M. bovis BCG* infection as compared to the soluble antigen PPD.*

Modulation of the extracellular matrix is a crucial component of inflammatory cell recruitment and pathology. Matrix metalloproteases (MMPs) are a family of endopeptidases that play a crucial role in matrix remodelling and in the activation of key molecules of the immune system including L-selectin, IL-6 and TNF. Marianne Quiding-Jarbrink has now demonstrated that phagocytosis of mycobacteria is a potent stimulus for secretion of active MMPs (particularly MMP-9 and -2) by murine macrophages *in vitro*. This process is rapid, occurring within 12 hours of infection and is most likely cytokine-driven, since induction can be inhibited by neutralization of TNF $\alpha$ .

It had previously been reported that the immune response to *Leishmania donovani* is organ-specific, the liver being a site of acute, resolving infection, whereas a chronic infection is established in the spleen and bone marrow. Work in Paul Kaye's group continues to explore how the immune response is initiated in these different organs, concentrating on the role of dendritic cells and costimulation. Recently, Chris Engwerda's laboratory has found that in visceral leishmaniasis splenic T cells are very susceptible to programmed cell death (PCD; apoptosis). Both intrinsic changes in splenic T cells during VL and signals from antigen-presenting cells from infected spleens contribute to this phenomenon.

#### POPULATION-BASED IMMUNOLOGY

Two important observations regarding mechanisms of clinical immunity were made during the year in Eleanor Riley's laboratory. Firstly, data from studies of malaria-endemic populations confirmed the general hypothesis that clinical immunity to malaria is associated with down-regulation of inflammatory cytokine responses. In a study in Ghana, susceptibility to clinical malaria was clearly linked to the propensity to produce high levels of the cytokines IL-12 and IFN $\gamma$ , whilst clinical immunity was associated with down-regulation of these responses. Secondly, also in Ghana, a longitudinal analysis of infection and antibody data from 200 children showed clear associations between decreasing maternal antibody levels and increasing risk of malaria

infection. However, it is also clear that some children carry persistent malaria infections and that these infections are kept below the threshold for triggering clinical disease, either in the presence or absence of detectable malarial antibodies.

Investigations in The Gambia by Geoffrey Targett and colleagues on the impact of different drug combinations on transmission of malaria showed that Fansidar treatment enhanced the release of gametocytes, which were infective to mosquitoes. Transmission was also achieved after treatment with drug combinations containing artesunate, which is thought to be gametocytocidal, though the number of gametocytes produced was greatly reduced. After drug treatment, blood samples containing only gametocytes were obtained and RT-PCR is being used to express genes coding for PfEMP 1, the rif/stevor multigene family, and CLAG, another family of genes linked with cytoadherence.

Emilia Valadas has been investigating cytokine production in tuberculosis, in collaboration with Francisco Antunes and Fernando Ventura (Centro de Malaria e Outras Tropicais, Lisbon). Patients with clinical tuberculosis often show depressed production of Type 1 cytokines and this was confirmed with blood samples from patients with pulmonary tuberculosis. Patients with extrapulmonary tuberculosis proved to have even lower IFN $\gamma$  production, while secretion of TNF $\alpha$  was raised. Other work by Sara Atkinson and Emilia Valadas in London has been investigating TNF $\alpha$  production by individual monocyte-derived macrophages using fluorescent-labelled mycobacteria and intracellular flow cytometry. Within infected cultures, non-infected as well as infected macrophages make TNF $\alpha$ , presumably triggered by products released by the infected cells.

Hazel Dockrell's group is also involved in larger immunoepidemiological studies. As part of a Wellcome Trust-funded programme with Paul Fine (Infectious Disease Epidemiology Unit), a BCG vaccination study is under way in Malaŵi, where BCG vaccination has been shown to provide protection against leprosy, but not tuberculosis. A total of 633 subjects were recruited in the first year of this project, two-thirds of whom were BCG vaccinated, with the remainder receiving placebo. Gillian Black is testing both T cell and monocyte responses to a wide range of mycobacterial antigens, to dissect the immunological changes induced by BCG vaccination. All the subjects are being followed up one year later, and a parallel study in UK schoolchildren, who are protected against tuberculosis by BCG vaccination, will start in 1999.

#### VACCINE DESIGN

Research into the development of vaccines against respiratory syncytial virus (RSV) and measles virus (MV) infections in Mike Steward's laboratory has focused on two major areas, namely the development of epitope-based DNA vaccines and of peptide-based vaccines. Plasmid DNA vectors have been constructed with minigenes encoding a single cytotoxic T-cell



(CTL) epitope from either the M2 protein of RSV or from the nucleoprotein of MV with or without a signal sequence. Protection against MV-induced encephalitis and reduction in viral load following RSV challenge was significantly enhanced in the presence of a signal sequence. These results highlight the ability of epitope-based DNA immunization to induce protective immune responses to well-defined epitopes and indicate the potential of this approach for the development of vaccines against infectious diseases.

Previous work had shown that RSV-specific cytotoxic T lymphocytes (CTL) or neutralizing antibodies can protect against RSV infection when induced separately by immunization with synthetic peptides. In work performed this year, RSV-specific neutralizing antibodies and CTLs were induced following immunization with a cocktail of peptides consisting of a B-cell mimotope (S1S-MAP), a T-helper epitope (SH: 45-60) and a CTL epitope linked to a fusion (F) peptide (F/M2: 81-95) comparable to those induced by the peptides alone. Following challenge, a 190-fold reduction in RSV titre and significantly reduced cellular infiltration in the lungs was observed following peptide cocktail immunization. The combination of RSV-specific humoral and cellular immunity induced by the peptide cocktail was thus more effective at clearing RSV than peptide-induced humoral or cellular immunity alone.

John Stephenson began a new research collaboration (with Dr J Nokes, Warwick University, and Dr W Ayele in Addis Ababa) designed to shed light on an important problem in controlling measles, i.e. the inability of very young children to be protected by conventional measles vaccine. The work is at an early stage, but should determine how the humoral immune response of young infants differs from that of adults (in this case their own mothers) thus giving clues about how to design better vaccines for very young children.

Andrei Timofeev (Russia) and John Stephenson have been developing some powerful new vectors aimed at studying the immune response to dengue and a related encephalitic disease, tick-borne encephalitis. Recent exciting results demonstrate that defective recombinant adenoviruses induce a Th1-like immune response and thus can be used as novel vaccines against these important diseases. Furthermore these results are strengthened by the observation that natural virus

infections are very poor at inducing anti-inflammatory cytokines, suggesting possible therapeutic interventions for these important diseases.

A main research interest of the molecular helminthology group is in schistosomiasis vaccine development. EC-supported work on the major Asian parasite *Schistosoma japonicum* has reached the stage where we are testing recombinant and DNA vaccines in the natural domestic animal reservoir hosts in China. Also in China, and with an eye to eventual clinical vaccine trials, we are carrying out investigations of antibody and cytokine responses against our 'candidate vaccine antigens' using serum and cells from *S. japonicum* patients with predefined levels of naturally-acquired immunity. Our collaborating partners in this work are Dr J-M Grzych and Professor A Capron (Institut Pasteur, Lille), Dr H Bogh and Professor P Nansen (Royal Agricultural and Veterinary University, Copenhagen), Professor Shi Fuhui (Chinese Academy of Agricultural Sciences, Shanghai), and Professor Zhang Zhaosong (Nanjing Medical University), and the cytokine analysis is being performed in close collaboration with Rosemary Weir and Hazel Dockrell.

#### DRUG DISCOVERY

The WHO/TDR supported group has identified several groups of compounds with novel antiprotozoal activity including terpyridine-platinum (II) complexes against *Leishmania* and *Trypanosoma cruzi* (with Professor G Lowe, University of Oxford), glutathione derivatives against *T. brucei* (with Dr C D'Silva, Manchester Metropolitan University), trypanothione reductase subversive substrates against *Trypanosoma* and *Leishmania* (with Dr E Davioud, Institut Pasteur, Lille) and apicidin derivatives against *T. brucei* (with Dr J Murray, GlaxoWellcome, Cambridge). An immunomodulator, tucaresol, has shown significant activity against *L. donovani* in models of infection (with Dr J Rhodes, GlaxoWellcome, Stevenage). Research on new amphotericin B formulations has continued with arabinogalactan conjugates (with Dr J Golenser, Hebrew Haddassah Medical School, Jerusalem) and heat-modified drug (with Professor J Bolard, Université Pierre et Marie Curie, Paris) showing improved activity against experimental leishmaniasis and lipid formulations having activity against *T. cruzi* infections.

#### RESEARCH DEGREE STUDENTS

**Marco Albonico** (Italy). Evaluation of effective strategies for the control of morbidity due to intestinal nematodes.

**Peter Axton** (UK). Cytokine function in the regulation of cell recruitment in pulmonary cryptococcosis.

**Shweta Brahmhatt** (UK). Human T cell responses to *Mycobacterium leprae* peptides.

**Sara Cotterell** (UK). Chemokine function in visceral leishmaniasis.

**Patricia Escobar** (Colombia). Interaction between drugs and the immune response in leishmaniasis and trypanosomiasis.

**Silvia Fejzo Bino** (Albania). Antisense complementary peptides as cytokine inhibitors.

**Shisong Jiang** (China). Peptide vaccines against RSV.

**Muthoni Junghae** (Kenya). *Leishmania*/drug interactions and macrophage activation.

**Fatima Kazi** (UK). The role of NK cell-derived cytokines in immunity to tuberculosis.

**Magita Khalouha** (UK). Nutritional status in ballet dancers.



**Ganjana Lertmengkolchai** (Thailand). Mechanisms of cell mediated immunity to *Burkholderia pseudomallei*.

**Sangeeta Matu** (Denmark). Studies on anti-leishmanial alkyllysophospholipids.

**Paul Morrison** (UK). Cellular immune responses induced by chimeric virus particles expressing measles virus epitopes.

**Wieslawa Olszewska** (Poland). Antibody responses induced by chimeric virus particles expressing measles virus epitopes.

**Diane Ordway de Abreu Pereira** (USA). Cytotoxic role of  $\gamma\alpha$  T cells to immunity against tuberculosis and HIV infection.

**Nicholas Pugh** (UK). Disease associations of the novel human herpesvirus, HHV-8, in immunocompromised and non-compromised subjects.

**Martin Sanchez Silva** (Venezuela). T-cell receptor usage in visceral leishmaniasis.

**Pitak Santanirand** (Thailand). Cytokine responses and immunity to *Burkholderia pseudomallei* in vitro and in vivo.

**Steven Smith** (UK). The role of antigen-specific CD8+ T cells in immunity to tuberculosis.

**Emilia Jesus Encarnacao Valadas** (Portugal). Human cytokine responses induced by *Mycobacterium bovis* BCG.

**Anong Wongsriraksa** (Thailand). Identification of antigens of *Burkholderia pseudomallei* reactive with patients' antibodies in melioidosis.

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#### THESES

CHIRINOS-ROJAS C. (Venezuela) *Use of combinatorial peptide libraries to identify inhibitors of the TNF induced cytotoxicity in vitro.* (PhD), 1998.

HAYAT S. (UK) *The effect of serum amyloid A on some high density lipoprotein functions* (PhD), 1998.

HSU S-C. (Taiwan) *Induction of Respiratory Syncytial Virus-specific cytotoxic T-cell responses by synthetic peptides in mice.* (PhD), 1998.

MALIN A. (UK) *Vaccinia expression of Mycobacterium tuberculosis antigen 85 and ESAT-6 secreted proteins* (PhD), 1998.

MURPHY M. (UK) *The role of costimulatory molecules during murine visceral leishmaniasis* (PhD), 1998.

SMELT S. (UK) *The role of B lymphocytes in murine visceral leishmaniasis* (PhD), 1998.



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The Unit conducts research on the epidemiology and control of infectious disease of public health importance. Work is carried out both in developing countries and in industrialized countries including the UK. Research ranges from ecological studies of variations in disease frequency in different populations, through observational cohort and case-control studies to define risk factors for disease, to randomized controlled trials to test the impact of specific preventive and curative interventions.

The Unit has major field research programmes in Malaŵi, Tanzania and the UK, and numerous collaborative projects in other countries in Africa, Asia and Latin America. Major interests include HIV and other sexually transmitted diseases, tuberculosis and other mycobacteria, malaria and other tropical parasites, hepatitis, measles and other vaccine-

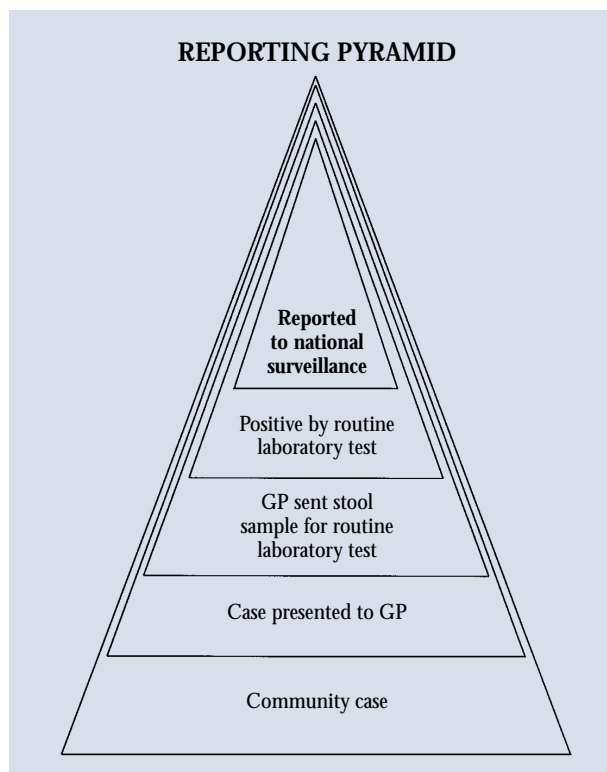
preventable diseases, respiratory diseases and gastro-intestinal infections. Methodological research is carried out on statistical methods, transmission models, genetic epidemiology and immunoepidemiology. The Unit is a WHO Collaborating Centre for the clinical evaluation of vaccines in developing countries.

#### INFECTIOUS INTESTINAL DISEASE IN ENGLAND

In collaboration with the Public Health Laboratory Service, a study of the incidence of infectious intestinal disease (IID) in the community, the proportion of cases presenting to their general practitioner (GP) and their microbial aetiology was conducted in 70 practices recruited from the MRC General Practice Research Framework. The study, based on 7000 person-years of observation, estimated that 9.4 million cases of IID occur in England each year, of which only 16%



consult a GP. The most frequently detected pathogen in the community was Small Round Structured Virus (SRSV). Other pathogens, notably *Campylobacter*, *Salmonella* and Rotavirus, were more common in cases presenting to GPs. Despite comprehensive laboratory testing, no target pathogen was detected in 45% of GP cases. Only one in every 136 cases in the community was reported through the national laboratory reporting system. The proportion reported varied by pathogen, and was higher for major bacterial pathogens (1 in 3 for *Salmonella*, 1 in 8 for *Campylobacter*) than for viral pathogens (1 in 35 for rotavirus, 1 in 1562 for SRSV). The overall cost of IID in England was estimated to be £743 million per year. Results concerning risk factors for IID will be published later this year.

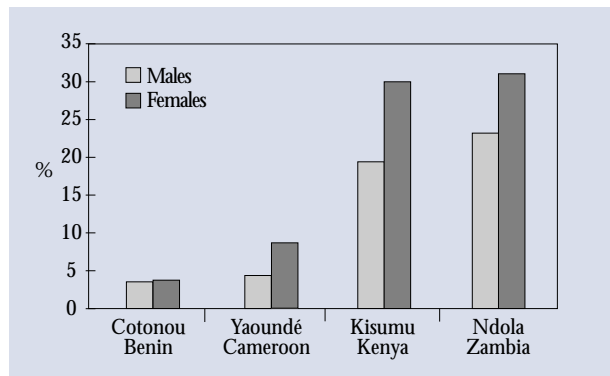


*Reporting pyramid for cases of IID occurring in the community.*

#### HETEROGENEITY OF HIV EPIDEMICS IN AFRICAN CITIES

A cross-sectional study to investigate reasons for the large variations in HIV prevalence between different African cities has been carried out in collaboration with the Institute of Tropical Medicine, Antwerp, INSERM Unit 88, CEPED, UNAIDS, and colleagues in four African cities: Cotonou, Benin; Yaoundé, Cameroon; Kisumu, Kenya; and Ndola, Zambia. Standardized instruments, including a detailed questionnaire and testing of blood and urine specimens, were used to collect information on possible risk factors from random population-based samples of 2000 adults and 300 commercial sex workers in each city.

HIV prevalence was much higher in Kisumu and Ndola than in Cotonou and Yaoundé. Overall prevalence was significantly higher in women than men in each city except



*HIV prevalence in four African cities.*

Cotonou. The difference was most striking among 15-24 year olds, with prevalences among women in Kisumu and Ndola of 30% and 28% respectively. There were no clear differences between high and low prevalence cities in patterns of sexual behaviour, except that the proportion of women reporting sex before age 15 was higher in Ndola and Kisumu. However in the high prevalence cities, most men were uncircumcised, and ulcerative STDs (syphilis and HSV-2) were more prevalent, particularly among young people. It seems likely that factors influencing the transmission probability per sexual contact play an important role in explaining the observed differences in HIV prevalence.

#### RESEARCH ON MYCOBACTERIAL DISEASES

A major research programme in Malaŵi is investigating the epidemiology of tuberculosis and leprosy and, in particular, reasons for the greater efficacy of BCG against leprosy than against tuberculosis in that environment. In addition to studies of genetic determinants of both diseases (with Professor A Hill, Oxford University), cellular immune responses to BCG are being investigated by analysing cytokine responses of whole blood to mycobacterial antigens, before and after BCG vaccination (with Hazel Dockrell (Immunology Unit) and Professor J Blackwell, (Cambridge University)). A similar study has just been initiated among schoolchildren in the UK, in order to compare responses in a population where BCG is known to protect against tuberculosis.

In Brazil, a major trial of a second dose of BCG vaccine is being conducted in almost 800 schools in two states. The Brazilian study also includes immunological measures comparable to those employed in the Malaŵi and UK studies.

The Unit is also working on mathematical modelling of tuberculosis dynamics. This research has provided important insights into the role of reinfection in populations with high transmission risks, and into the special properties of reproduction number statistics under conditions in which infection risks change over time and reinfection can occur. Unit staff are collaborating with scientists in the Netherlands to model the molecular epidemiology of tuberculosis, with particular reference to problems of estimating the rate of change of the *M. tuberculosis* genome (molecular clock speed).



### DATA-DERIVED ALGORITHMS FOR VERBAL AUTOPSIES

The verbal autopsy (VA) is a widely used method for collecting information on cause-specific mortality where medical certification of deaths is incomplete. Trained fieldworkers interview bereaved relatives to elicit information on symptoms experienced by the deceased before death. Causes of death may be assigned by following an expert algorithm. School staff have conducted validation studies in adults and children, which have shown the accuracy of VA to vary by disease and setting.

Further research has explored whether statistical techniques might yield more accurate algorithms than those proposed by clinical experts. Data were drawn from a validation study of 796 adult deaths occurring at hospitals in Tanzania, Ethiopia, and Ghana. The leading causes of death were tuberculosis/AIDS (19%), malaria (11%), meningitis (8%), and cardiovascular disorders (8%). The data-derived algorithms were found to be as accurate as the expert algorithms. Both approaches accurately assigned deaths due to tuberculosis/AIDS and meningitis, but neither worked as well for malaria or cardiovascular disorders.

### AEROSOL MEASLES VACCINES

More than one dose of vaccine is necessary for the sustained control of measles. In collaboration with the South African Medical Research Council, the University of Natal, the UK Public Health Laboratory Service, the Mexican Ministry of Health and the Task Force for Child Survival and Development, Atlanta, a randomized trial of the administration of a second dose of vaccine by different routes was conducted in Durban from 1995-8. Schoolchildren aged

5-14 years were randomized to receive standard titre doses of either Schwarz or Edmonston-Zagreb (EZ) measles vaccines either subcutaneously or by aerosol.

Among 992 children followed to one year post-revaccination, antibody levels were highest in the EZ aerosol group. Only 4% of children in this group were seronegative one year post-vaccination, significantly fewer than in the EZ subcutaneous (9%) or Schwarz subcutaneous (14%) groups. The Schwarz aerosol group performed poorly, and its reconstituted vaccine lost potency quickly in the nebulizer. This research has shown that the aerosol route using currently available devices and a suitably stable vaccine is effective and acceptable. It is readily adaptable to mass campaigns, avoiding the risks of unsafe injection practices. Further evaluation of the aerosol route for the delivery of measles and other vaccines is in progress in Mexico.

### CREUTZFELDT-JAKOB DISEASE

The Unit continues to collaborate with the National Creutzfeldt-Jakob Disease Surveillance Unit and the Neuropathogenesis Unit in Edinburgh. Unit staff serve on the Spongiform Encephalopathy Advisory Committee (SEAC) and on a subgroup charged with investigating how predictions of future case numbers should be made. Work examining the spatial distribution of variant-CJD cases with respect to meat rendering plants was completed, finding no convincing evidence that residence close to such plants was associated with increased risk of the disease. An analysis of the lifetime residential histories of sporadic and variant CJD cases to look for evidence of clustering prior to disease onset was begun and will be completed shortly. Unit staff continue to conduct routine analyses of surveillance data and case-control data on potential risk factors for CJD.

### RESEARCH DEGREE STUDENTS

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**Ana Luiza de Souza** (Brazil). Epidemiology of tuberculosis, BCG and atypical mycobacteria.

**Peter K Borus** (Kenya). Response to measles vaccine in HIV infected infants.

**Benson Chilima** (Malawi). Natural history of environmental mycobacteria in Karonga District, northern Malawi.

**Tobias F Chirwa** (Malawi). Implications of household dynamics for the risk of infection associated with household contact.

**Pornthip Chompoon** (Thailand). Surveillance and aetiology of *Shigella* infections in Thailand.

**Jean-Paul Guthman** (France). A case-control study to determine risk factors for acute febrile malaria in the Pura valley, Peru.

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**Alessia Melegaro** (Italy). Measuring the transmissibility of infections.

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## THESES

- GRANT AD. (UK) *Spectrum and natural history of HIV disease in Abidjan, Côte d'Ivoire*. (PhD), 1998.
- ZAMAN SMA. (Bangladesh) *Cohort study of the effect of measles on childhood morbidity in urban Bangladesh*. (PhD), 1998.

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## PATHOGEN MOLECULAR BIOLOGY AND BIOCHEMISTRY UNIT

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Unit staff seek to understand molecular and biochemical processes in pathogens, in the context of devising new strategies for disease control. Research interests include: post-genomic research initiatives; virulence factors and pathogenesis; evasion of immune response; drug resistance; population genetics; recombinant vaccines; development of genetic manipulation techniques; molecular diagnostics, and the transfer of relevant technologies to the disease-endemic areas. Present efforts are focused on malaria; *Mycobacteria* and *Chlamydia*; herpesviruses; trypanosomatid parasites; amoebiasis; and haemorrhagic fever viruses.

### MOLECULAR VIROLOGY

Human herpesviruses (HHV) research focuses on the newly described HHV-6 and HHV-8. These viruses are associated with AIDS-related illness as well as with pathology in the immunocompetent host. The complete genomic sequence for HHV-6 has been established. Post-genomic analyses are in progress to characterize vital components that determine infection, evasion of immunological recognition and persistence in cells normally mediating protective immunity. Genes encoding viral glycoprotein complexes essential for virus infection have been identified. These act by mediating cellular fusion. The site of their interaction has been defined, showing that it is required for a fusin-associated conformation and for detection by antibodies that prevent infection. Recombinant adenovirus technology is being used to investigate further the relationship of glycoprotein complexes to cell fusion in comparisons with the related human cytomegalovirus (HCMV). Novel virus members of the immunoglobulin superfamily have been characterized, which are antigenic and can enhance infection by cellular fusion. New HHV-6 G-protein coupled receptors (GCRs) have also been characterized, which can act as chemokine receptors, may participate in immune evasion and are co-opted by HIV as co-receptors. HHV-6 GCR causes down regulation of specific chemokines, which is important as these ligands initiate an inflammatory response. An HHV-6 specific chemokine-like molecule has been identified and shows regulation by novel splicing. Latency is another strategy to escape host immunity: a potential latency regulator, which can repress virus DNA replication, has been found.

Further collaborative studies in Zambia have demonstrated novel strain variants of HHV-6/-7 and HHV-8. This includes finding unusual childhood infections with the rare AIDS-related variant A of HHV-6 and with a new strain group of HHV-8. The HHV-8b strains identified in infant infections are related to those in HIV-negative childhood endemics of Kaposi's sarcoma (KS) as well as to strains circulating in the now more prevalent AIDS-related epidemic KS.

Research on dengue fever has demonstrated the role of the virus NS1 protein in immune evasion and in disease pathogenesis, identified new candidate vaccine epitopes, and developed systems for screening mosquitoes for infection, genotyping viruses and predicting epidemics (in collaboration

with the Disease Control and Vector Biology Unit (DCVBU)).

### BACTERIAL PATHOGENESIS

The global tuberculosis situation is deteriorating, despite revised treatment strategies. The availability of the *Mycobacterium tuberculosis* genome sequence now gives basic information to produce a quantum leap in understanding of biology of the pathogen. The Unit has focused attention on two aspects of efficient genetic approaches to exploitation of the genome sequence.

Firstly, ways have been developed to improve the efficiency of targeted mutagenesis. The ability to knock genes out 'at will', an important way of understanding gene function, has been difficult in *M.tuberculosis*. Pre-treatment of the DNA used to transform *M.tuberculosis* has been shown to increase the rate of homologous recombination, and this has allowed inactivation of an hemolysin gene. The methodology has since been refined to simplify cloning, speed up analysis of transformants, and to produce several more mutants, which are currently being assessed for loss of virulence.

Secondly, a Wellcome Trust-funded collaborative project has begun, based at St George's Hospital, to produce an *M.tuberculosis* microarray. The microarray will consist of all 4000 *M.tuberculosis* genes spotted onto a glass microscope slide. *M.tuberculosis* mRNA hybridized to the slides as fluorescently-labelled cDNA will give an overall picture of transcription. This approach also allows comparison of patterns of transcription under different growth conditions and, in relevant mutants, gives a detailed picture of patterns of gene expression.

The biology of inositol, an essential component of mycobacteria, is also a research interest. The structure of inositol monophosphate phosphatases is being compared with the human homologues (with Dr N McDonald, Imperial Cancer Research Fund).

Research on *Chlamydia* molecular pathogenesis has also entered the post-genomic era and has been focused on two parallel projects: studies of type III secretion in *Chlamydia psittaci* and *C.pneumoniae*, and studies on the role of a gene family (*pmp* genes) in adaptation to environmental conditions in *C.trachomatis*. Recombinants have been generated and their products purified for the purpose of producing antibodies for cell biology studies and for the evaluation of human immune responses to the relevant chlamydial antigens. Professor Byron Batteiger, on a sabbatical from Indiana University, cloned and expressed several of the *pmp* genes from a genital strain of *C.trachomatis*. Counterparts of these genes have also been cloned from an ocular strain. These new tools will allow us to focus on the structure-function relationship of these proteins, their possible role in *Chlamydia* pathogenesis, and their potential in immune protection. Major new funding was obtained to



support and expand research on *Chlamydia*, from BBSRC, Wyeth-Lederle, and the British Heart Foundation.

### MALARIA RESEARCH

Studies on the genetics of *Plasmodium falciparum* have confirmed that there is frequent meiotic recombination in natural populations, so that genetic association (linkage disequilibrium) between different polymorphic nucleotide sites declines rapidly with increasing molecular distance between the sites. Mapping of sequence sites under natural selection in antigen genes involves comparisons with non-coding polymorphic microsatellite allele frequencies for statistical purposes. For one major candidate antigen site under selection, evidence is emerging from a large immunoparasitological study of allele-specific protective immune responses. Further work on the population genetics of *Plasmodium* is focused on the full sequence of the small mitochondrial genome, to identify the genetic relationships among haplotypes of *P.falciparum* and the closely-related species *Preichenowi*.

As part of an investigation of the role of cyclic nucleotide signal transduction in *P. falciparum*, several key genes involved in transduction pathways have been isolated. Guanylyl cyclase enzyme activity has been demonstrated in the products of two of these genes (with Pauline Schaap, The Netherlands). This activity is probably associated with a novel, bifunctional integral membrane protein. Gene deletion experiments (with Alan Cowman, Australia) will investigate the biological function of these enzymes as a step towards assessing their potential as drug targets.

It has been shown that a combination of two polymorphisms in *P.falciparum* *Pfmdr-1* and *Cg-2* genes predicts chloroquine resistance with 75% sensitivity and 100% specificity in Zaria, West Africa. This points the way towards using molecular techniques to monitor chloroquine resistance. In a study at a hypoendemic malaria site near Mount Kenya, 23/34 malaria cases requiring hospital admission had Tyr-86 and Tyr-1246 polymorphisms in *Pfmdr-1*. Two polymorphisms in DHPS and three in DHFR, which predict sulfadoxine/pyrimethamine resistance, were also seen in parasite material from these cases. This observation suggests that drug resistance may be an important factor in severe malaria in this epidemic region (with Professor D Gump, Vermont).

### AMOEBIASIS RESEARCH

*Entamoeba histolytica* lacks recognizable mitochondria but contains genes encoding proteins of mitochondrial origin. One of these proteins has been localized to a previously undescribed organelle of putative mitochondrial origin, the mitosome. Most cells contain only one mitosome, as determined by immunofluorescence studies. The importation of proteins into the mitosome has been shown to follow a pathway similar to that seen in mitochondria. The structure and function of the organelle in *E.histolytica* is now being investigated.

### TRYPANOSOMATID RESEARCH

The Unit has a strong input into the WHO *Trypanosoma cruzi* genome project. This in part involves the design of techniques that will allow gene function to be studied at a genome wide level, thus fully exploiting the genome sequence data. To this end chromosome-fragmentation vectors have been constructed to identify rapidly essential genes that may serve as targets for new chemotherapeutic agents, and to study chromosome structure and maintenance.

Trypanosomatids are exposed to different environments during their life-cycles. It is essential that they possess mechanisms to respond to these changes; these differentiation steps may be mediated by the adenylate cyclase (ADC) system. In *T.cruzi* ADC conforms to the 'receptor-type' (distinct from that of the host) and is expressed by a complex multigene family. High levels of the catalytic domains have been expressed in *E.coli*, and they are active in the absence of accessory factors. A second approach to studying regulatory mechanisms in *T.cruzi* has been initiated with the isolation of a gene (*bpp1*) that encodes a novel member of the b-propeller family of regulatory proteins.

Interest in oxidative defence of *T.cruzi* is focused on mechanisms of peroxide metabolism. It has been shown that in *T.cruzi* this process is compartmentalized with distinct cytosolic and mitochondrial systems. Transformation-mediated overexpression of peroxiredoxin enzymes confers increased resistance to exogenous peroxides.

The major surface molecules of the invasive forms of *T.cruzi* are a heterogeneous family of mucin-like glycoproteins. The role of the hyper-variable domain of these proteins in immune evasion is being determined. This involves the expression of tagged forms of these proteins in transformed parasites. The function of cruzipain, the major cysteine proteinase of *T.cruzi*, and the possible role that it may have in the pathology of Chagas' disease is also under investigation.

The genetic manipulation of yeast, as a model system, and of trypanosomes, has been used to investigate the molecular control of antigenic variation in the African trypanosome *T.brucei*. Antigenic variation allows these parasites to persist in chronic infections, causing diseases such as sleeping sickness in humans and nagana in cattle. Several mutant strains are being tested for defects in gene expression and in antigenic variation.

A serendipitous discovery demonstrated that the anti-influenza drug rimantadine was highly effective at killing bloodstream forms of *T.brucei*. Rimantadine is therefore a representative of a class of prospective trypanocidal drugs.

Research on trypanosomatid genetic diversity has produced the first experimental evidence of genetic exchange in *T.cruzi*, of naturally occurring hybrids between *Leishmania* species in Peru (in collaboration with DCVBU), and demonstrated that



Old World *L.infantum* and New World *L.chagasi* are indistinguishable at the molecular level, which suggests common approaches to disease control.

### INSECT MOLECULAR GENETICS

Microsatellite DNA markers have been developed as a tool for population genetic analysis of *Anopheles arabiensis*. They are being applied to a population in Northern Kwazulu, which retreats in the dry season to a few widely scattered permanent water holes. Using microsatellite data we have looked at population structure and found evidence of limited migration within the region. This suggests that insecticide

treatment of these small and clearly defined dry season foci could limit or even prevent the normal rainy season expansion. This year larvicide was applied during the dry season to selected breeding sites. Microsatellite markers will be used to measure the impact upon local genetic diversity in the vector population.

A new research initiative (in collaboration with Dr CB Beard, CDC, Atlanta) will explore the molecular taxonomy and population genetics of triatomine bugs in the context of expanding vector control programmes for Chagas' disease into northern South America and Central America.

### RESEARCH DEGREE STUDENTS

Fernando Abad-Franch (Spain). Epidemiology of *Rhodnius ecuadoriensis*.

Clare L Allen (UK). Organization and expression of the genes encoding the mucin-like glycoproteins of *Trypanosoma cruzi*.

Zubaida D F Al-Suwaidi (Qatar). Investigation of rapid methods for drug susceptibility testing of mycobacteria.

Christina Bakatselou (Greece). Heat shock protein genes of *Entamoeba histolytica*.

Elizabeth V Bromley (UK). Functional analysis of G protein related molecules in *Trypanosoma cruzi*.

Nicola Casali (UK). Molecular genetics of environmental adaptation in *Mycobacterium tuberculosis*.

Nabeela Dhiban (United Arab Emirates). Simultaneous diagnosis of several faecal protozoa by PCR-based methods.

Manoj T Duraisingh (India). Artemisinin-resistance in *Plasmodium falciparum*.

Sandrine Ferrand (France). Glutathione reductase in *Plasmodium falciparum*.

Alexandra K Ingram (UK). VSG expression in *T.brucei*.

Frances C Kasolo (Zambia). Molecular studies of novel herpesviruses and HIV in paediatric infections in Zambia.

Isabel L Mauricio (Portugal). Genetic diversity in the *Leishmania donovani* complex.

Nadine Mozzato Chamay (Italy). Polymorphisms in genes encoding cytokines and proteins involved in transcriptional regulation: importance as disease determinants.

David Muhia (Kenya). Novel targets for antimalarial chemotherapy.

Deborah Nolder (UK). Molecular diversity in the *Leishmania* subgenus *Viannia*.

Sabah Omar (Kenya). Drug resistance in malaria in Kenya.

Christopher M Parry (UK). Molecular identification, characterization and processing of the human herpesvirus-6 protease.

Carey Pashley (UK). Identification of essential mycobacterial genes.

David A Paterson (UK). Use of recombinant adenovirus in characterization of the gH/gL complex and membrane fusion mediated by beta-herpesviruses, human cytomegalovirus and human herpesvirus 6.

Jonathan C P Steele (UK). Anti-plasmodial plants.

Adriana Tami-Hirsch (Venezuela). Malaria among Yanomami and Yekwana ethnic groups.

Mariela Torres-Torres (Colombia). Triatomine molecular taxonomy.

Simon J Turner (UK). The characterization of HHV-6 cis-acting sites in replication and use as a vector for gene expression/therapy studies.

Mehreen Zaki (Pakistan). Identification of polymorphic DNA markers in *Entamoeba histolytica*.

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## THESES

- KASOLO FC. (Zambia) *Molecular studies of novel herpesvirus and HIV in paediatric infections in Zambia*. (PhD). 1998.
- PARRY CM. (UK) *Molecular identification, characterization and processing of the human herpesvirus-6 protease*. (PhD). 1998.

## DEPARTMENT OF PUBLIC HEALTH AND POLICY

## HEAD OF DEPARTMENT

**Professor Nicholas A Black** MD FFPHM DCH DRCOG (*from 1.5.98*)**Professor Charles EM Normand** BA DPhil (*to 30.4.98*)

## DEPARTMENTAL ADMINISTRATOR

**Douglas Brooker** (*from 4.12.98*)**Hong-Yoke Lim** BA (*to 3.12.98*)

## DEPARTMENTAL SECRETARY

**Cari Caldwell** (*from 1.12.98*)**Karen Jelf** (*from 1.5.98 to 30.11.98*)**Samantha Mann** (*to 30.4.98*)

## COMPUTING TEACHING OFFICER

**Barbara Neville** BA BSc

## COMPUTING OFFICERS

**Mick Hussey** BA MSc**Caroline Fernyhough** BSc

## TEACHING SECRETARY

**Gwenda Hoare**

## VISITING PROFESSORS

**Sir Donald Acheson**

KBE MA DM MD DSc LLD FRCP FRCS FFPHM FFO

**Sheila Adam** MD FFPHM MRCP**Rasaratnam Balarajan** MBBS DPH MSc FFPHM**Jack Cuzick** BSc MSc PhD**Alain C Enthoven** BA MPhil PhD**David Fine** BA MHA**Spencer Hagar** MB ChB DPH PhD MA MFCM FFPHM**Nicholas Mays** BA HonFFPHM**Richard Smith** BSc MB ChB MSc

## EMERITUS PROFESSORS

**Jerry Morris** CBE MA HonDSc HonMD HonFFPHM**Patrick Vaughan** MD FRCP FFPHM

The Department houses the largest multidisciplinary group in Europe conducting public health and health policy research. All the relevant disciplines are well represented – 19 epidemiologists, 12 public health physicians, 7 statisticians and mathematicians, 21 economists, 12 policy analysts, and 38 from other social sciences including anthropology, sociology, history, psychology, demography and geography. In addition, key health care professions (doctors, nurses, pharmacists) are represented. This wide range of disciplines is reflected in the research methods used which include qualitative (such as documentary analysis, in-depth interviews and non-participant observation) and quantitative techniques (such as randomized trials, predictive modelling and psychometrics).

Staff are as concerned about their research being of relevance to practice and policy as it being of high academic quality. This is reflected in the many diverse ways staff collaborate with other organizations – government departments both in the UK and overseas, non-governmental organizations, professional associations (such as the Royal Colleges), health service providers, and international bodies (such as the World Bank, WHO, and the European Commission). In addition, members of the Department provide advice on a consultancy basis to many organizations around the world.

A feature of the Department's research is a keen interest and involvement in methodological issues. This includes: the development and testing of health outcome and risk adjustment measures; techniques for geographical analyses; the development of health indicators for specific diseases and community-based indicators for environmental health; costing methods and economic evaluation techniques; comparison of randomized and non-randomized evidence;

methods for assessing the quality of non-randomized studies; the use of consensus development methods; modelling incident need from prevalence data and the amount of population health gain from preventive and curative interventions; and methods for evaluating health promotion.

Another common thread that runs through all four units in the Department is concern about the interface between scientific research and practice or policy. This is being explored both historically and through several contemporary projects both in developed and developing countries.

There were several major initiatives during 1998. First, we are contributing to the second National Survey of Sexual Attitudes and Lifestyles in the UK. Second, staff organized a highly successful international meeting on 'Reforming Health Sectors' (the School's 8th Annual Public Health Forum). Third, the importance of the economic aspects of infectious disease was recognized in the establishment of an inter-departmental Collaborative Centre for Economics of Infectious Diseases. Fourth, the establishment of the Department of Health-funded National Centre for Health Outcomes Development jointly with the University of Oxford. Fifth, the launch of the European Observatory on Health Care Systems, jointly with several organizations including WHO and the World Bank. Finally, our longstanding programme of research on, and audit of, surgery was consolidated with the establishment of the Clinical Effectiveness Unit at the Royal College of Surgeons of England. Future initiatives include developments in primary care research, health impact assessment and risk analysis, and studies of globalization.

The Department continues to grow. During 1998 our staff



included 5 professors, 3 readers, 20 senior lecturers and 22 lecturers. In addition there were 46 research fellows, 7 research assistants, 36 administrative and clerical staff, and 5 staff carrying out computing tasks. Ben Armstrong took over as Head of the Environmental Epidemiology Unit and Helen Dolk acted as Research Degree Director for six months.

The research degree programme also continues to expand. Apart from 16 members of staff, we had 88 students from 38 countries registered for higher research degrees, including 3 DrPH (Doctor of Public Health) students. During the year, three PhDs were awarded and the theses titles are included in each Unit's list of publications.

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## ENVIRONMENTAL EPIDEMIOLOGY UNIT

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BC Cancer Agency

British Council for the  
Prevention of Blindness

British Heart Foundation

British Lung Foundation

Colt Foundation

Commission of the  
European Communities

Department of Health

Foundation for the Study of  
Infant Deaths

Health Education Authority

Joseph Rowntree Foundation

National Asthma Campaign

NHS Executive

Nuffield Foundation

Nuffield Institute of Health

Occupational Health  
Services, AIVO CanadaPublic Health Laboratory  
ServicesSingapore Eye Research  
Institute

University of Surrey

The Wellcome Trust

World Bank

The Unit carries out research in environmental epidemiology and environmental health policy. Through the epidemiological study of groups subject to putative environmental health risks, we seek to evaluate whether the risks are real, and if so to quantify them. We also aim to inform the development of environmental health policy by studying perceptions of risks and attitudes towards them, and by undertaking health risk assessments of policy implications based on current knowledge. Further, we develop methods pertinent to research in this field. Unit staff have a wide variety of skills, reflecting the interdisciplinary nature of much of our research. These include epidemiology, statistics, policy analysis, anthropology, computing, and geographic information systems.

**EXCESS WINTER MORTALITY AND HOUSING**

It has long been known that in Britain mortality in winter months is some 20% higher than the rest of the year. The

reasons for this, however, are poorly understood. The fact that the winter excess is higher in Britain than that in many countries with colder winters suggests that many of these premature deaths are avoidable. In a series of studies, researchers in the Unit are investigating the specific conditions under which excess of winter mortality is high. In recently completed research, it was found most of the winter excess was explained directly by cold temperatures, with daily mortality rising by some 2% for every degree centigrade that mean maximum daily temperature in the preceding two weeks dipped below 19°. This is consistent with our earlier finding that people living in homes without central heating had greater risk of death in winter. Ongoing research seeks to identify more precisely the relationship between temperature and mortality, and the way in which housing factors affect it.

**AIR POLLUTION**

Air pollution, a central concern in environmental health, is



the subject of several of the Unit's projects. In particular, the Unit co-ordinates a six-country Central European Study of Air Pollution and Respiratory Health, together with colleagues from RIVM in Bilthoven and the Agricultural University in Wageningen. Preliminary combined analyses show higher rates of respiratory symptoms in countries with higher levels of air pollution, but within country analyses are much less consistent. Full analyses using multilevel modelling techniques, currently under way, are investigating these contrasting patterns.

An investigation of leukaemia rates in enumeration districts in south-east England in relation to estimated emissions of benzene was completed. Initial results showed a strong positive association. However, careful analysis showed this to be influenced by a few 'clusters' of cases with residential addresses very close to major hospitals. Checking showed that these were in fact unlikely to be real addresses and removal of them from analyses showed a much weaker association – an experience with wide implications for this method.

#### ENVIRONMENTAL HEALTH POLICY

It is well known that environmental changes will affect countries differently, necessitating different policies for different regions. It is also well known that policy contexts differ internationally and that policymakers will react differently to environmental health research. Researchers from the Unit, in collaboration with the Stockholm Environment Institute and contributors from a number of developing countries, examined the impacts of environmental change on human health in African, Caribbean and countries that are signatories to the Lomé Convention. Results indicated that food security and unhealthy living environments are key issues of environmental change in such countries. The review guides environment and health practitioners and policy makers on strategies to achieve intersectoral agendas.

Also completed was a policy study on the use of environmental health information in the development of policies to reduce inequalities in health. This suggests the strategic importance of study design and dissemination of

research on inequalities – and patience. Further, in collaboration with the Robens Institute and the Ministry of Health in Uganda, the Unit has assisted in the development of methods of monitoring urban water supply that focus on priority groups from a health perspective.

#### CONGENITAL MALFORMATIONS

The Unit continues its work looking at the risk of congenital anomalies among residents living near hazardous waste landfill sites. The first results (showing a 33% excess risk among those living close to the sites) were published in 1998, generating huge media and public interest and debate as to what the appropriate policy reaction should be. Research on the geographical distribution of anophthalmia/microphthalmia was also published (showing no localized clustering but an excess in rural areas), and this work continues. We have also looked at the prevalence of various adverse perinatal outcomes in relation to economic status – a focus of interest for other research in the Unit. One project found that the level of deprivation of the area in which a mother lives predicts low birthweight even after allowing for individual social class, suggesting that the economic circumstance of a neighbourhood contributes to maternal health. We have started work on the epidemiology of hypospadias, in response to observations that the prevalence of hypospadias has been increasing and that this may be associated with exposure to endocrine-disrupting chemicals. This work analyses existing surveillance data on hypospadias in UK and Europe.

#### LEUKAEMIA AND MAGNETIC FIELDS

Members of the Unit have been responsible, in collaboration with Canadian researchers, for the analysis of a large Canadian case-control study of childhood leukaemia. First results show, in contrast to some earlier reports from the USA and Scandinavia, that in Western Canada and Quebec children living in strong magnetic fields were no more likely to contract leukaemia than those living in weaker fields. This is despite the fact that field levels were rather higher in this study than others. The study will play an important part in several reviews of this question currently under way or planned.

#### RESEARCH DEGREE STUDENTS

**Araceli Lorraine Busby** (UK). Clustering and geographical variation in anophthalmos/microphthalmos.

**Romulo Paes De Sousa** (Brazil). Environmental epidemiology and policy.

**Iliana Del Rio-Gomez** (Mexico). Organochlorines and endometriosis.

**Hyacinth Thorne Domonic Roberts** (Grenada). Infectious waste management.

**Miguel San Sebastian** (Spain). Health impact of oil companies in Ecuador.

**Mi-A Son** (Korea). Occupational epidemiology.

**Ronald Dollete Subida** (Philippines). Environmental risk assessment.

**Yih-Jian Tsai** (Taiwan). Hazards exposure.

**Ferdinando Emanuele Vegni** (Italy). Respiratory disease and air pollution.

**Martine Vrijheid** (Netherlands). Risk of congenital malformations.



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- Dixon J, Sanderson CFB, Elliott P, WALLS PH, Jones J, Petticrew MP. Assessment of the reproducibility of clinical coding in routinely collected hospital activity data: a study in two hospitals. *Journal of Public Health Medicine* 1998; **20**:63-69.
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## HEALTH POLICY UNIT

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<b>Patrick Vaughan</b> MD FRCP FFPHM	Emeritus Professor	<i>Health Care Epidemiologist</i>	
<b>Gill Walt</b> BSc PhD	Reader	<i>Health Policy</i>	
<b>Susan Foster</b> MA PhD	Senior Lecturer	<i>Health Economist</i>	
<b>Julia Fox-Rushby</b> BSc PhD	Senior Lecturer	<i>Health Economist</i>	
<b>Lucy Gilson</b> MA PhD	Senior Lecturer	<i>Health Economist</i>	
<b>Barbara McPake</b> BA PhD	Senior Lecturer	<i>Health Economist</i>	
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<b>Ruairi Brugh</b> DCH DipObs MSc MFPHMI MD	Lecturer	<i>Public Health Physician</i>	
<b>Hilary Goodman</b> BA MA	Lecturer	<i>Health Policy</i>	
<b>Lilani Kumaranayake</b> BA MA PhD	Lecturer	<i>Health Economist</i>	
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<b>Jessica Ogden</b> BA MA PhD	Lecturer	<i>Social Anthropologist</i>	
<b>Dinesh Sethi</b> MDCCP MD MSc MFPHM	Lecturer	<i>Public Health Physician</i>	
<b>Charlotte Watts</b> BA MSc PhD	Lecturer	<i>Epidemiologist/Health Policy</i>	
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The Unit aims to inform and strengthen the development and implementation of health policy and to increase understanding of the process of policy development. Areas of expertise include health policy analysis, health systems

research and health economics, with an emphasis on low- and middle-income countries. Staff come from disciplines ranging from sociology, social policy and political science, to anthropology, mathematical modelling and epidemiology.



There are four substantive areas of activity: health economics and financing, infectious disease policy, globalization, and conflict and health. Our cross-cutting concerns focus on poverty and inequity, public health problems and interventions, the policy implications of ageing populations, gender and the role of the for-profit private health care sector.

### INFECTIOUS DISEASES POLICY GROUP

The impetus for the group arose from a concern that despite knowledge that health reflects a complex interaction between biology, culture and human activity, emphasis is often put solely on the biological dimension. The group brings together what we know about these other influences to explore the interaction of biological with socio-cultural factors. By developing this approach we can better understand common obstacles to effective policy including poverty, inequity, environmental decline, limited access. This knowledge can be used to enhance the relationship between individuals and communities with health structures, as well as to devise practical solutions to infectious disease problems.

During the year, group members have been involved in developing a wide range of research activities on various dimensions of infectious disease policy, including the transfer of policies from the international to the national level, new partnerships in the control and treatment of infectious diseases, and the acceptability and accessibility of services.

### DFID HEALTH ECONOMICS AND FINANCING PROGRAMME

1998 marked the final year of the second phase of this programme. Notable successes included a successful triennial review by the funder, DFID and the award of a contract for another 5-year programme, 1999-2004. This ensures the medium-term future of a large volume of activities, supported in addition by a variety of other funders.

Anne Mills organized the School's 8th Annual Public Health Forum *Reforming Health Sectors*, which drew together researchers, policy makers and practitioners to review the increased knowledge of health sector reform issues that has accrued over the last 10 years. Around 200 participants from almost 50 countries attended, including many of our collaborators who participated as speakers. In association with the Forum the Unit ran workshops on health care financing reform in Latin America, on donor co-ordination and on post-conflict health sector recovery.

Work on equity and user fees has featured strongly in the programme. A study was completed of the Thai system for exempting the poor from health care fees, one of the very few systems which is thought to work reasonably well. The study evaluated its performance and, drawing lessons from features which were conducive to effectiveness, this work should be of value to other countries.

The economics of malaria is an increasingly important part of

our work. We completed research on improving knowledge about the cost-effectiveness of control measures in order to inform the international Roll Back Malaria programme. Using modelling, we were able to demonstrate that highly cost-effective interventions are available. The for-profit private sector in low- and middle-income countries is a focus of our research, both from a health economics perspective looking at regulation and social marketing and from a public health perspective, to evaluate the potential for improving the quality of care delivered by private providers for public health priority diseases. Substantial progress was made in finalizing 'HIV Tools', which is developing methods to assess the cost-effectiveness of different HIV prevention strategies. Programme staff moderated a Web-based discussion on the cost-effectiveness of HIV prevention, which attracted global interest and improved our understanding of the value of new technologies for communication.

### CONFLICT AND HEALTH

The Unit provides the base for promoting research and teaching on the impact of conflict on health and health systems, the role of public health in humanitarian emergencies and in post-conflict recovery. There is a considerable gap between research and policy in this area and we have much to offer in partnership with governments, NGOs, donors and where feasible, affected communities. Teaching modules have been developed with academic institutions in Spain and Britain to reflect key policy concerns with conflict and the international humanitarian response.

Work on reproductive health and conflict was completed which emphasized the centrality of involving affected communities in influencing the response to humanitarian emergencies and chronic conflicts. A related project explored the emergence of policy regarding reproductive health in emergencies. An ongoing project, with World Bank support, aims to build planning and policy-making capacity in countries emerging from periods of conflict. Emphases were on promoting equity, identifying information needs for policy-making, building human resource capacity, and developing NGO-state relationships.

Particular effort has focused on understanding the evidence-base upon which public health responses to humanitarian emergencies should be based; to this effect a partnership with Medical Emergency Relief International (MERLIN) was established, funded by the Andrew Mellon Foundation. This initiative will collate evidence regarding public health practice in emergencies and will work towards deriving good practice and effective mechanisms of implementing these through linking academic and NGO practitioners.

### GLOBALIZATION

A number of projects around globalization and health have been initiated. The Nuffield Trust funded two projects aimed at informing UK policy of the impacts of globalization on health including one focusing on public health measures



concerned with transborder health risks. A second project, *Global health: a local issue* is a policy review bringing together senior policy makers and researchers to consider the implications of globalization for health in the UK.

WHO's Tobacco Free Initiative has funded the development of a political mapping study in middle- and lower-income countries that will provide a better understanding of the political environment at country level, where the proposed Framework Convention on Tobacco Control will seek to have

its greatest impact. Unit staff are contributing to a Rockefeller Foundation/WHO/Society for International Development initiative, *Globalization: Rethinking equity and health*, and the development of a WHO work programme on globalization and health, both of which will yield new agendas for research and policy. We are collectively writing a book entitled *Crossing boundaries: health policy in a globalizing world* which explores how globalization affects the nature and process of health policy making.

### RESEARCH DEGREE STUDENTS

**Mohammad Amin** (Bangladesh). An analysis of the private sector health care market and its regulation in Bangladesh

**Eddas Bennett** (USA). Cost-effectiveness of local health authorities in South Africa.

**Mrigesh Bhatia** (India). Economic evaluation of malaria control in Surat, India: bednets vs residual insecticide spray.

**Joao Costa** (Brazil). Health demands from an industrial complex and the development of a private health care market in the Metropolitan Region of Salvador, Bahia State, Brazil.

**Nile El Wardani** (USA). Defining the role and function of the WHO country representative: a worldwide survey (a study in the changing roles of international agencies and their influence on national policy and programme implementation).

**Ibrahim Elziq** (UK). Assessment of the health insurance needs of the Palestinian people.

**Alejandra Gonzalez-Rossetti** (Mexico). Political dimensions in health sector reform.

**Mir Ajmal Hamid** (Pakistan). Regulation of the private health care sector in Pakistan.

**Charles Hongoro** (Zimbabwe). An evaluation of decentralization of health services in Zimbabwe: the rationale, process, impact and public sector efficiency.

**Niyada Kiatying-Angsulee** (Thailand). Model for auditing and improving drug authority in registration and regulation of pharmaceuticals in the country: the case study of Thailand.

**Nassor Kikumbih** (Tanzania). Estimating public gain from an insecticide-treated net programme: The case of Kilombero sugar factory.

**Julia Kilbourne** (USA). Kenyan horticulture workers: policy implications and strategies for attaining healthier conditions.

**Masahide Kondo** (Japan). Equity under prepayment financing scheme in rural sub-Saharan Africa.

**Sukhontha Kongsin** (Thailand). Policies to mitigate the economic and social impact of HIV/AIDS morbidity and mortality on households in northern Thailand.

**Stanley Lalta** (Trinidad). Privatization in the Jamaican health sector: case study of contracting hospital support services.

**Jwo-Leun Lee** (Taiwan). Health insurance.

**Jongkol Lertindumrong** (Thailand). The evaluation of health reform: the case of civil servant medical benefit scheme in Thailand.

**Xingzhu Liu** (China). The impact of doctor payment reform on the efficiency of hospital services: a case study in PR China.

**David McCoy** (Malaysia). Health systems organizations and management in the context of decentralization.

**Omer Mensah** (Benin). The financing of health programmes in Benin: the national malaria programme and the Bamako Initiative.

**Mario Mosquera** (Colombia). Interface between health services and communities within the health sector reform in Colombia.

**Mercy Mugo** (Kenya). Economic evaluation of school-based interventions in control of helminth infections in Kenya.

**Thelma Narayan** (India). National programme on TB in India: policy development and implementation.

**Obinna Onwujekwe** (Nigeria). Economic analysis of a community-controlled system for financing and delivering an incremental health package for the control of onchocerciasis and malaria in onchocerciasis-endemic areas of south-eastern Nigeria.

**Junko Otani** (Japan). Health policy for societies with rapidly ageing populations.

**Manisri Puntularp** (Thailand). Economic evaluation of malaria volunteers in Thailand.

**Kent Ranson** (Canada). The consequences of health insurance for the informal sector: Three non-governmental, non-profit schemes in Gujarat.

**Sandra Reyes-Frausto** (Mexico). Policies for the elderly in Mexico.

**Steven Russell** (UK). Ability to pay for health care.

**Nordin Saleh** (Malaysia). The privatization of medical screening for foreign workers in Malaysia.

### PUBLICATIONS

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## HEALTH PROMOTION RESEARCH UNIT

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<b>Gert Knerer</b> MA MSc	Research Fellow	<i>Epidemiologist</i>	
<b>Kelly Loughlin</b> MA PhD	Research Fellow	<i>Historian</i>	
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The Unit is a multidisciplinary group bringing together expertise in epidemiology, anthropology, sociology, social history, economics and computer modelling. The aims of the Unit are to conduct research to inform health promotion policy, to evaluate health promotion initiatives and to

emphasize and analyse the links between research, policy and practice in this area. Our interest in approaches to the evaluation of health promotion has resulted in a forthcoming book arising out of a series of Unit workshops on the subject to which many Unit members have contributed



(M Thorogood and Y Coombes(eds) *Evaluating health promotion*. OUP, 1999. ISBN 0192631091).

### SEXUAL HEALTH

The AIDS Public Health Information Exchange continues to bring together materials and assessments from AIDS education programmes in different countries in the European Union and the former Soviet bloc, facilitating the exchange of ideas and information. Studies are under way examining HIV testing in Europe and HIV prevention interventions for gay men. In the UK, the National Survey of Sexual Attitudes and Lifestyles (NSSL II) is in progress and analysis of the data will begin in 2000. Studies are being undertaken on variations in the prevalence of teenage conceptions in Europe and on population estimates of unintended conceptions in the UK. The portrayal in the media of sexual health issues is being investigated. Ethnographic research in India on sex work and the local context of an HIV-prevention project has been completed and another study on men who have sex with men is in preparation.

A multidisciplinary team has developed and piloted SASHI (Situational Analysis for Sexual Health in India) which was a method of collecting socio-behavioural and epidemiological information needed to design interventions for STD/HIV prevention and control. A user-friendly implementation package is nearing completion.

### WOMEN'S HEALTH

In the Middle East, the Unit has been co-ordinating a regional network to maximize Arab maternal health (the MAMAH network). Two studies have aimed to evaluate and improve maternal and child health services to Palestinians in Gaza and Bedouin Arabs in the Negev. One output will be a book which discusses the nature and function of research in the shadow of the peace process.

In Bangladesh, an anthropological study is exploring the factors affecting quality of care in obstetric facilities. Meanwhile, the Unit has been collaborating with the Drug Safety Research Unit, University of Southampton, on a large case-control study of the risk of heart attacks in users of modern oral contraceptives. This has shown that the risk associated with such use is small, but that cigarette smoking considerably increases a young woman's risk.

### CHRONIC DISEASE PROBLEMS

The Health Gain project (jointly with the Health Services Research Unit) explores the effectiveness and resource implications of strategies for reducing the burden of chronic disease, in particular cardiovascular disease and cancers. Studies within this project include two trials of exercise promotion, a study of the costs involved in coronary heart disease prevention and treatment, an exploration of the potential benefits of using disease-specific contracts for commissioning cancer treatment services, and a meta-analysis of dietary interventions in the population. An evaluation of a

community intervention to increase awareness of the health effects of smoking and to reduce the prevalence of smoking in the Turkish-speaking community in Camden and Islington, was carried out. The core of the project is computer modelling to produce useful predictions of the relative cost-effectiveness of interventions.

A cost-effectiveness analysis of different approaches for screening for familial hypercholesterolaemia is being conducted. It compares the effects of population versus cascade (case finding) strategies and a clinical versus a genetic diagnosis. There is considerable potential to reduce the mortality and morbidity from this condition through early diagnosis and treatment. Cause-specific mortality attributable to current alcohol consumption levels in the UK is being calculated. The effects of age, gender, beverage type and pattern of consumption are being incorporated into the estimates.

Many of these issues of chronic disease are the province of primary health care which is central to UK government health policy. There is an emerging primary care group in the Unit consisting of three local general practitioners whose main interests are in managing coronary heart disease and drug misuse. Other research on drug misuse in the Unit includes an historical study, an evaluation of a dance/drugs project, and a prison research project to guide the introduction of harm reduction measures designed to reduce transmission of HIV and other effects of unsafe injecting. The latter has provided the research component to a pilot study of the provision of disinfecting tablets in prisons.

Members of the Unit are collaborating with the Department of Community Medicine, University of Witwatersrand, South Africa on an anthropological and epidemiological study of the health burden of hypertension, diabetes and stroke in rural South Africa. In Europe, a case study approach is being used to develop a model of 'best practice'. Major achievements in relation to health indices in specific areas, alcohol for example, are related to contributory factors.

### SCIENCE AND POLICY

The relationship between research and policy is central to many activities in the Unit and staff seek to disseminate their findings to policy makers and others. The nature of the science/policy relationship and its change over time is the focus of an historical programme of work set in the UK in the post-war period. Its case studies are smoking; illicit drugs; nutrition policy and especially the relation between diet and heart disease; renal dialysis and intensive care; and the role of the media. Our concern is how a scientific 'fact' becomes a policy 'truth' and the complex web of expertise, activism, economic, cultural and political factors which determine the inter-relationship. Other research is on the oral history of community and hospital pharmacy. The history group also held a conference which brought together historical and contemporary interests in public health research.



## INEQUALITIES IN HEALTH

A project on the meaning of socio-economic position in relation to ethnicity and health status has the aim of developing valid comparative methods for measurement of socio-economic position within and between different ethnic groups. Qualitative and survey research among Afro-

Caribbeans, South Asians and whites, together with secondary analysis of existing data sets, is being undertaken in collaboration with colleagues at Bradford and Bristol universities. The history group is also looking at the issue of inequality from an historical perspective.

### RESEARCH DEGREE STUDENTS

Paul Boyce (UK). Sexual behaviour in India.

Julie Bronson (USA). Nutrition in the Bahamas.

Gillian Burn (UK). Worksite health programmes.

Tony Cutler (UK). Cost of the NHS.

Catrin Evans (UK). Commercial sex work and sexual health in India.

Carmen Garcia-Pena (Mexico). Chronic diseases and ageing.

Fadia Hasna (Jordan). Reproductive health in the Middle East.

Melissa Hersh (USA). Law and ethics in biomedical research.

Ariel King (USA). Pharmaceutical policy in South Africa.

Margaret Leppard (UK). Obstetric care in a Bangladesh.

Efstratia Simou (Greece). HIV/AIDS.

William Stewart (UK). HIV/AIDS education in China.

Helena Tuomainen (Finland). Nutritional behaviour comparative study.

Ann-Karin Valle (Norway). Inequity in health.

Emma Wilkinson (UK). The value of health promotion to business.

Kate Wood (UK). Sexual, reproductive health in South Africa.

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## THESIS

KINGMA MMF (Switzerland) *Economic policy: incentive or disincentive for community nurses?* (PhD), 1998.

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1999

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Professor

Professor &  
Head of Department (from 1.5.98)

Professor &  
Head of Department (to 30.4.98)

Reader

Senior Lecturer

Senior Lecturer

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Audit Commission

British Association of Plastic  
Surgeons

British Telecom plc

Bromley Health Authority

Commission of the  
European Communities

Department of the  
Environment

Department for  
International Development  
(DFID)

Department of Health

Economic and Social  
Research Council

European Investment Bank

Government of Hungary

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Know-How Fund

Medical Research Council

NHS Executive

Nuffield Trust

Public Health Laboratory  
Service

Royal College of Surgeons of  
England

The Wellcome Trust

World Bank

World Health Organization

UNICEF

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1999

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The Unit aims to provide rigorous evidence to be used to improve the effectiveness, efficiency, equity and humanity of health care, largely through better decision-making, service delivery and organization. Our approach is multidisciplinary, uses quantitative and qualitative methods, and involves the range of organizational levels from direct providers of care to international policy-makers. It is underpinned by methodological development and work on the dissemination of research and new technologies. The context is mainly middle- and high-income countries.

Close contacts with decision-makers are essential, and many academic staff have joint or honorary appointments with the NHS. Senior staff contribute to expert advisory committees at regional, national and international levels, through the Royal Colleges, Department of Health and other national bodies, WHO, the European Union and the World Bank. Most of this advice relates to determining research priorities or to strengthening the influence of research on policy.

### HEALTH OUTCOMES

Methodological studies continue on the development and validation of instruments for assessing health outcomes. With earlier work now completed on patient-assessed measures of outcome in prostatectomy, menorrhagia, maternity services, neurological disability, chronic venous diseases and ocular disease, progress is now being made on measures of outcome in coronary revascularization, plastic surgery, multiple sclerosis and sino-nasal surgery. At a more macro level, the shortage of indicators of the quality of ambulatory care has led to the development of a set of 'Ambulatory-Care-Sensitive' conditions. The hypothesis is that low admission rates for this set of conditions is indicative of good quality ambulatory care, and vice versa.

The National Centre for Health Outcomes Development (formerly the Central Health Outcomes Unit) moved from the Department of Health and is now based jointly at the School and the University of Oxford. It is a key source of

information on health and health outcomes at many levels for the NHS in England and for the Government. Its work includes: analysis, publication, dissemination and evaluation of existing indicators and proxy measures of health outcomes; development and evaluation of new indicators; development of an electronic Clinical and Health Outcomes Knowledge Base; commissioning developmental projects to fill in key gaps; and promotion of the use of such knowledge for planning, management and monitoring interventions to improve health and for policy development. In this last context, the Centre is funding a project based jointly in the Unit and at Southampton University to develop a microsimulation model. This will support the evaluation of policy options in the field of services for coronary heart disease, and contribute to the next round of the NHS National Service Framework.

### EFFECTIVENESS, EFFICIENCY AND EQUITY

Evaluation studies continue to be a major activity in the Unit. Current work includes: the evaluation of the costs and benefits of dialysis in the elderly; the cost-effectiveness of primary care in the prevention of heart disease; decision-making in prophylactic oophorectomy; outcomes in surgery for stress incontinence; and the diagnosis and management of vestibular dysfunction. Studies of equity and access address treatment for end-stage renal failure in Romania, the use of health care in Chile, and the effect of gender on use of diagnostic and therapeutic interventions in England.

The Royal College of Surgeons' Clinical Effectiveness Unit (CEU) was established in 1998 as a collaboration between the College and the School. Its primary focus is the collection of high quality data describing surgical treatment and health outcomes. These data are used for clinical audit, and for developing prognostic indicators that can be used *inter alia* as a basis for case-mix adjustment when making inter-hospital comparisons. The CEU hopes to play a major role in the work of the National Institute of Clinical Excellence.



## RESEARCH EVIDENCE AND CLINICAL PRACTICE

Whilst actively developing critiques of evidence-based medicine, staff have undertaken systematic reviews of: the effectiveness of groin hernia surgery; consensus development methods for creating clinical guidelines; randomized versus non-randomized designs for health care evaluation; cardiovascular disease and heavy drinking; outcomes in intensive care; and models of care for A&E. Other studies have included a randomized trial of blinding and unmasking in peer review of manuscripts and the development of a national consensus on priorities for intensive care research in the UK.

The Centre for Policy in Nursing Research, a joint initiative with the Royal College of Nursing (RCN), provides a co-ordinated strategy for research in nursing, midwifery and health visiting and disseminates 'good' research practice. Current and future work includes setting research priorities in conjunction with the RCN and other key stakeholders, a bibliometric analysis of nursing research activity, the dissemination of nursing research by policy-makers and practitioners, and capacity-building approaches by research funding and commissioning organisations. The Centre is also involved in research on nursing roles and a cross-national study of hospital restructuring and patient outcomes.

## SERVICE DELIVERY AND ORGANIZATION OF HEALTH CARE

Studies include: an evaluation of *The Health of the Nation*; an evaluation of partnerships for health strategy in the new NHS; a comparison of integrated and non-integrated trusts; managed markets; the contracting process; inter-agency working in injury reduction; and the management of epidemiological emergencies that cross borders in Europe. These studies are part of a broader agenda of research into service delivery and organization which will be developed further in the future.

## ECONOMICS OF INFECTIOUS DISEASE

Completed studies include the socio-economic aspects of salmonella, intervention strategies for hepatitis B and C, hospital-acquired infection and *E. coli* O157. Further studies are well advanced in intestinal infectious disease, lower respiratory tract infections and syphilis prevention. Economic aspects of surveillance and the impact of contractual arrangements on the public health function are also being addressed. Ongoing work includes studies of the risks of infectious disease in managed markets, hepatitis C in haemophilia patients, and interventions to delay the onset of liver diseases associated with hepatitis C. The Collaborative Centre for Economics of Infectious Diseases, a joint initiative with the School's Department of Infectious and Tropical Diseases and the Public Health Laboratory Service and several national and international organizations, was established during 1998.

## CENTRAL AND EASTERN EUROPE

The Unit has a major focus on health and health care in Eastern Europe, through the European Centre on Health of Societies in Transition (ECOHOST), a WHO Collaborating Centre created jointly with the Department of Epidemiology and Population Health. ECOHOST is undertaking a wide range of studies across the region encompassing the health consequences of German reunification, studies of nutrition and smoking patterns in, among others, the Baltic republics, Russia and Bulgaria, trends in mortality in the former Soviet Union, and birth outcomes and injury policy in several countries undergoing transition. ECOHOST also hosts part of the European Observatory on Health Care Systems, jointly with the WHO, the World Bank, the European Investment Bank, the London School of Economics and the Governments of Spain and Norway. This is producing a series of detailed overviews of health care systems in Europe and analytic studies of issues such as the future role of the hospital.

### RESEARCH DEGREE STUDENTS

**Oscar Arteaga** (Chile). Relationships between public and private health care in Chile.

**Dina Balabanova** (Bulgaria). Financing the health care system in Bulgaria – models for development.

**Jane Brooks** (UK). University education for nurses.

**Elizabeth Butters** (UK). Testing outcome measures in the routine practice of HIV/AIDS community palliative care services.

**Arthur SC Chern** (Singapore). The market for physicians in Singapore.

**Lesley Duff** (UK). Measuring satisfaction with maternity services for women from ethnic minorities.

**Steven Farmer** (USA). A comparative international study of interventions during the last year of life for elderly patients with advanced disease.

**Alison Frater** (UK). Reducing the burden of breast cancer in England and Wales.

**Peter Gaal** (Hungary). Financial incentives, physician behaviour and health care reforms in Hungary.

**Cesar Gattini** (Chile). Equity and efficiency in the provision of care in decentralized public health services.

**Richard Hatchett** (UK). Nursing history.

**Duangtip Hongsamoot** (Thailand). Inspection: a vehicle to improve use of medicines in private pharmacies.

**Jeremy Hobart** (UK). Measurement of neuro-rehabilitation outcomes.

**Gabor Hoffer** (Hungary). Priority setting for public health services in Hungary.

**Sang-Hyo Kim** (S.Korea). Health services in Korea.

**Susan Law** (UK). Setting priorities in the NHS.

**Richard Lewis** (UK). Reorganization of primary care in London.

**Diane Morin** (Canada). Comprehensive geriatric assessment.

**Ellen Nolte** (Germany). Explaining the health divide in east and west Europe: the German situation.

**Catherine Pope** (UK). The practice of surgery.

**Aziz Rahman** (Bangladesh). Evaluation of primary care development in Bangladesh.

**Mala Rao** (UK). Development of a measure of quality of care for older people in general practice.

**Balazs Rekassy** (Hungary). Reforming Hungarian primary health care.

**Magda Rosenmoller** (Germany). Critical success factors of technical assistance projects in the health sector in central and eastern Europe.



**Franco Sassi (Italy).** Economic appraisal and technology diffusion.

**Serdar Savas (Turkey).** Contracting in health care.

**Andreea Steriu (Romania).** Management of end stage renal failure in Romania.

**Ruth Stern (UK).** Can communities be effective partners?

**Rosanna Tarricone (Italy).** Economic evaluation of treatment for depression.

**Roqayyah Taqi (Kuwait).** Improving asthma medical documentation for paediatric patients presenting to emergency room in Kuwaiti hospitals.

**Zsuzsa Varvasovszky (Hungary).** Alcohol policy and prevention in Hungary.

**Susan Volker (UK).** Palliative care.

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## HOW TO BECOME A RESEARCH STUDENT AT THE SCHOOL

The London School of Hygiene & Tropical Medicine provides training in research at three levels: as a component of the taught MSc courses, at the post-doctoral level to Research Fellows, and most particularly to doctoral students doing their PhD or DrPH research based at the School. This brief account is for readers of the Research Report who are particularly interested in one of the areas of work described and who may wish to pursue research training to doctoral level at the School. There are both formal and informal aspects of exploring this further. The formal aspects concern possession of the entrance requirements, having a source of funding, and completing a formal application to the School. The Deputy Registrar (*e-mail: registry@lshtm.ac.uk*) at the School can provide information on these matters and an application form. The address, fax and telephone numbers are given inside the front cover of this

Report. If you have the appropriate qualifications and a deep interest in a specific area of research, when submitting your official application it is also good to write informally, with your research proposal, to the appropriate Unit Head or staff member, to explore whether the School is the best base for your research and whether an appropriate supervisor is both available and has a vacancy.

It is a requirement for students to spend a minimum of nine months at the School, three of which must be at the beginning of the period of study and three at the end. In the case of laboratory work, it is common for the whole PhD to be carried out at the School. Many students in epidemiological and other subjects, however, do the field collection of data in the country relevant to their project.

## HOW TO BECOME A POST-DOCTORAL RESEARCH FELLOW

For those with doctoral qualifications, the varied Units within the School provide an excellent base for post-doctoral study in the many areas related to public health; the range of expertise and active seminar programmes provide a stimulating and broadening research atmosphere. Research Fellow posts may arise on grants held by staff members. These are advertised in the appropriate journals. Other post-doctoral researchers may

gain fellowships from their governments or other funding agencies. There is no single formal route to post-doctoral work; many contacts begin with scientific correspondence concerning research results or at a seminar or scientific meeting. Those interested should write initially to the Head or an appropriate member of the Unit doing the research of particular interest.

## BUILDING HEALTH RESEARCH CAPACITY GLOBALLY

The needs of the world for good health research are very great, and, especially in developing countries, there is a lack of institutional capacity, funds and trained research workers. While the research capacity and productivity of the London School of Hygiene & Tropical Medicine is substantial, it is minute in relation to current global needs for health research. The School is therefore particularly concerned to help build research capacity throughout the world, particularly in developing countries, and more recently in Central Europe. It does this in several ways. The most important is by training research workers through its MSc, doctoral and post-doctoral programmes. Its alumni now number many thousands and occupy key positions in organizations involved in health research throughout the world.

Traditionally, the School has felt free to collaborate with sister institutions worldwide and has not needed to have formal agreements on this. Scientists with common interests, or former students, all provide a necessary and sufficient basis for research collaboration and for helping to build research

capacity. But some overseas institutions, for reasons that may be bureaucratic or pragmatic and to facilitate flows of funds, need a more formal agreement with the School and this has been entered into with several institutions. The School increasingly finds itself involved in formal links to consolidate more spontaneous and informal contacts.

School staff have also played key roles in the increasing global moves to foster indigenous health research capacity in developing countries. Staff have been members of the research strengthening group of the WHO/UNDP/IBRD Special Programme for Research and Training in Tropical Diseases; and have played active roles in the Commission on Health Research for Development and its successors, in the work of UNICEF and of the World Bank to build research capacity and with many international organizations to help countries solve their own health research problems. The School is committed to this process of building research capacity and welcomes suggestions on how it can assist.

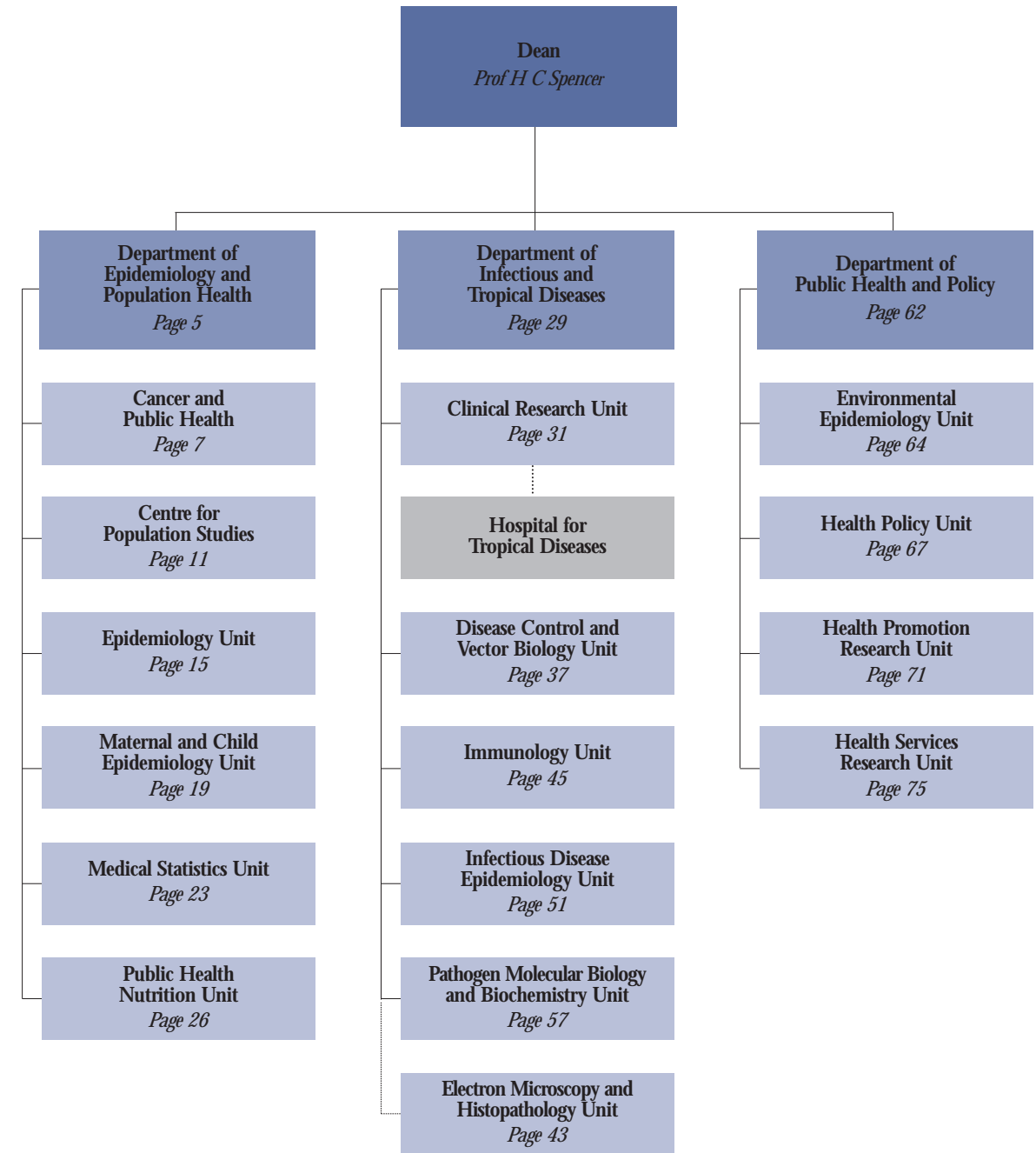


INDEXES

The School's approach to research is both multi-disciplinary and international. Moreover, there are several topics of such wide public health importance that they are studied by several Units. These pictorial indexes are intended to help the reader to identify Units interested in a particular topic, discipline or country, where that is not apparent from the Unit's

title. For example, a reader interested in demography would first look at the report from the Centre for Population Studies and then perhaps look at demography in the *Outline Index to Disciplines* and under appropriate topics in the *Outline Index to Research Interests of Units*.

ORGANIZATION



OUTLINE INDEX TO REGIONS

This table shows the main regions of the world (using the World Bank categories) with which each Unit is currently involved.

UNITS		Established Market Economies	Middle Eastern Crescent	Formerly Socialist Economies	India	China	Other Asia and Islands	Latin America and the Caribbean	Sub-Saharan Africa
EPIDEMIOLOGY AND POPULATION HEALTH	Cancer and Public Health	●				●	●		
	Centre for Population Studies	●				●	●	●	
	Epidemiology	●	●	●					
	Maternal and Child Epidemiology	●	●			●			
	Medical Statistics	●					●		
	Public Health Nutrition	●	●				●	●	●
INFECTIOUS AND TROPICAL DISEASES	Clinical Research			●	●	●	●	●	
	Disease Control and Vector Biology	●	●	●	●	●	●	●	
	Electron Microscopy & Histopathology	●							
	Immunology		●		●	●	●	●	
	Infectious Disease Epidemiology	●		●	●	●	●	●	●
	Pathogen Molecular Biology and Biochemistry	●	●	●			●	●	●
PUBLIC HEALTH AND POLICY	Environmental Epidemiology	●					●	●	
	Health Policy	●	●		●	●	●	●	
	Health Promotion Research			●		●	●	●	
	Health Services Research	●	●				●	●	

KEY

- Project/Field Work
- Research Students and/or Post-Doctoral Fellows





