the 1960s. Access was given to the employees' roll although employment details during the war were virtually non-existent. We think that the information gathering process when taken together with the records of the coroner and the histopathology review was as detailed as any other similar study in existence.

As the "non-exposed" group was classified as such by history it is obvious to most readers that we are unable to state how they acquired excessive amounts of amphibole fibres within their lung tissues. If these eight cases with high amphibole concentrations are deducted the rate of mesothelioma becomes 1.6 million a year which is similar to the generally estimated background rate.

Greenberg seems to be unaware that high aspect ratio amphibole fibres have been found in the pleura.¹ By contrast with animal studies, which rely on the administration of enormous doses and overload of the respiratory defences, human studies have been remarkably consistent in showing a strong association between amphibole exposure and mesothelioma whereas for chrysotile it has been weak or non-existent.² Even in chrysotile miners and millers, in whom there have been few mesotheliomas, the evidence indicates that they were related to tremolite rather than chrysotile exposure.^{3,4} To the best of our knowledge the forthcoming review of chrysotile by the *International Programme on Chemical Safety* will not present any new evidence although it might give a different opinion. Other reviews conclude that amphiboles have a much greater potency than chrysotile for producing mesothelioma.^{5,6}

A T EDWARDS

Royal Halifax Infirmary,
Halifax, Yorkshire

D WHITAKER

Queen Elizabeth II Medical Centre,
Perth, Western Australia

K BROWNE

Formerly Medical Adviser to Cape Industries,
Leicester House, North Creae, Norfolk

F D POOLEY

School of Engineering,
Division of Materials and Minerals,
University of Wales, Cardiff

A R GIBBS

Department of Histopathology and Environmental
Lung Disease Research Group,
Llandough Hospital,
Penarth, South Glamorgan

- 1 Boutin C, Dumortier P, Rey F, Viallat JR, De Vuyst P. Black spots concentrate oncogenic asbestos fibres in the parietal pleura. *Am J Respir Crit Care Med* 1996;153:444-9.
- 2 Gibbs AR. Role of asbestos and other fibres in the development of diffuse malignant mesothelioma. *Thorax* 1990;45:649-54.
- 3 Dufresne A, Harrigan M, Masse S, Begin R. Fibres in lung tissues of mesothelioma cases among miners and millers of the township of Asbestos, Quebec. *Am J Ind Med* 1995;27:581-92.
- 4 McDonald JC, McDonald AD. Chrysotile, tremolite and mesothelioma. *Science* 1995;267:775-6.
- 5 Health risks associated with chrysotile asbestos. Papers from a workshop held in Jersey, Channel Islands, 14-17 November 1993. *Ann Occup Hyg* 1994;38:397-646.
- 6 Meldrum M. *Review of fibre toxicology*. Sudbury: HSE Books, 1996.

Biomarkers of exposure to low concentrations of benzene: a field assessment

Editor—Ong *et al*¹ present data on the relation between concentration of benzene in ambient air and urinary muconic acid concentration. With the formula they provided in figure 3, the urinary concentration of muconic acid equivalent to exposure to 1 part per million (ppm) is 144.4 or 128.6

ng/mg creatinine, depending on whether log to the base 10 or natural log is used, respectively. This number seems to be very low compared with that given in many studies which are usually in the range of > 1000 ng/mg creatinine.^{2,3} It will be helpful if Ong *et al* could provide some explanation for this apparent discrepancy.

ERIC S JOHNSON

School of Public Health and Tropical Medicine,
Tulane University Medical Centre,
New Orleans, Louisiana, USA

- 1 Ong CN, Kok PW, Ong HY, Shi CY, Lee BL, Phoon WH, Tan KT. Biomarkers of exposure to low concentrations of benzene: a field assessment. *Occup Environ Med* 1996;53:328-33.
- 2 Lauwerys RR, Buchet J-P, Andrien F. Muconic acid in urine: a reliable indicator of occupational exposure to benzene. *Am J Ind Med* 1994;25:297-300.
- 3 Inoue O, Seiji K, Nakatsuka H, Watanabe T, Yin S-N, Li G-L, *et al*. Urinary t,t-muconic acid as an indicator of exposure to benzene. *Br J Ind Med* 1989;46:122-7.

Author's reply—The overall objective of our article¹ was to evaluate the usefulness of five commonly used biomarkers in low level (< 0.25 ppm) exposure to benzene and as stipulated in the conclusion all the biomarkers **were unable** to provide sufficient specificity for biomonitoring at the low concentration range. All data (figs 1-3) suggested that they are not to be used for estimation of exposure to low level environmental exposure to benzene, particularly < 0.25 ppm. Our earlier data²⁻⁴ showed that trans,trans-muconic acid could be useful for environmental exposure to benzene > 0.5 ppm; with a calculated exposure to 1 ppm benzene, about 0.9-1.7 mg/g creatinine would be expected at the end of eight hours of exposure.

CHOON-NAM ONG

Department of Community, Occupational, and
Family Medicine,
National University of Singapore

- 1 Ong CN, Kok PW, Ong HY, Shi CY, Lee BL, Phoon WH, Tan KT. Biomarkers of exposure to low concentrations of benzene: a field assessment. *Occup Environ Med* 1996;53:328-33.
- 2 Lee BL, New AL, Kok PW, Ong HY, Shi CY, Ong CN. Urinary trans,trans-muconic acid determined by liquid chromatography: application in biomonitoring of benzene exposure. *Clin Chem* 1993;39:1788-92.
- 3 Ong CN, Lee BL. Determination of benzene and its metabolites: application in biological monitoring of environmental and occupational exposure to benzene. *J Chromatogr* 1994;660:1-22.
- 4 Ong CN, Kok PW, Lee BL, Shi CY, Ong HY, Chia KS, *et al*. Evaluation of biomarkers for occupational exposure to benzene. *Occup Environ Med* 1995;52:528-33.

Offspring sex ratios and reproductive hazards

Editor—Weijin and Olsen¹ write: "A conception closely associated with ovulation has been suggested to result in more boys". There seems to be an error here because to substantiate this statement, these authors cite France *et al*² who write: "The birth sex ratio favored males when intercourse preceded ovulation/fertilization by two days or longer". Indeed the data of France *et al*² give some corroboration to the conclusion of Gray³ who, after a meta-analysis of human data, suggested that the regression of offspring sex ratio (proportion male) on time of insemination within the cycle is U shaped.

I have cited⁴ evidence that:

(1) There is a positive relation between offspring sex ratio and parental coital rate in several mammalian species (including humans).

(2) Under some models, coital rate would determine the time of fertilisation within the cycle.

(3) Distributions of the sexes within litters of several mammalian species suggest that P_{male} (the probability that a zygote is male) varies from one zygote to another within litters.

Interpretation of the data is not established, but it seems likely that the variation of P_{male} with time across the female cycle is partially controlled by the varying female hormone concentrations across that time. In particular such an interpretation can be construed to explain Weijin and Olsen's¹ report of a significant decline of offspring sex ratio with waiting time to pregnancy. This confirms the data of Renkonen⁵ and may be caused by the different mean times of fertilisation within the cycle associated with different coital rates (which decline very rapidly during the first year of marriage^{6,7}).

If I am right, the sexes of mammalian (including human) offspring are partially controlled by the hormone concentrations of both parents around the time of fertilisation.⁸ So deleterious environmental agents which are endocrine disruptors may show themselves in biased offspring sex ratios. Thus it may be expected that offspring sex ratios will be increasingly used as indicators of adverse occupational exposures to men and women.

WILLIAM H JAMES

The Galton Laboratory,
University College London,
Wolfson House,
4 Stephenson Way,
London NW1 2HE

- 1 Weijin Z, Olsen J. Offspring sex ratio as an indicator of reproductive hazards. *Occup Environ Med* 1996;53:503-4.
- 2 France JT, Graham FM, Gosling L, Hair P, Knox BS. Characteristics of natural conceptual cycles occurring in a prospective study of sex preselection: fertility awareness symptoms, hormone levels, sperm survival and pregnancy outcome. *Int J Fertil* 1992;37:244-55.
- 3 Gray RH. Natural family planning and sex selection: fact or fiction? *Am J Obstet Gynecol* 1991;165:1982-4.
- 4 James WH. Factors affecting sex ratios in mammalian offspring: follicular phase length, cycle day of conception and sex ratio of offspring. *Hum Reprod* 1995;10:2529-31.
- 5 Renkonen KO. Heterogeneity among first post-nuptial deliveries. *Ann Hum Genet* 1970;33:319-21.
- 6 James WH. The honeymoon effect on marital coitus. *Journal of Sex Research* 1981;17:114-23.
- 7 James WH. Decline in coital rates with spouses' ages and duration of marriage. *J Biosoc Sci* 1983;15:83-7.
- 8 James WH. Evidence that mammalian sex ratios at birth are partially controlled by parental hormone levels at the time of conception. *J Theor Biol* 1996;180:271-86.

BOOK REVIEWS

Book review editor: R L Maynard

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Handbook of Stress, Medicine, and Health, 1st ed. Edited by: CL COOPER. (Pp 338; price: £69.) 1996. Boca Raton, FL: CRC Press. ISBN: 0-8493-2908-6.

One of the aims of this handbook, declared by the editor in his preface, is to christen a new medical speciality: Stress Medicine. Cooper qualified in psychology and business studies in California and now holds the chair of organisational psychology at Manchester University's Institute of Science and Technology. He is coeditor of the journal *Stress Medicine*, and is well known for his many publications in this field.

The book constitutes a gold mine of references for anyone wishing to chart the development of the stress concept, from the early work of the physicians who noted that diverse physical challenges (such as noise, cold, heat, pain, toxins, blood loss, x ray films, etc) produced certain shared physiological disturbances in common. Hans Selye borrowed "stress" from engineering usage to denote these shared, non-specific distortions of normal functioning. This was an unfortunate choice, which has caused much confusion: to an engineer, it is the forces applied to a structure (a bridge for example) which comprise stress; the resulting distortion is known as strain. Selye used the wrong word. As he himself later acknowledged, "strain" would have been the right term. Nevertheless stress has persisted, albeit as something of a chameleon with shifting meaning. Today, the emphasis is towards pressures of a more psychological kind and stress has become a vogue word.

Most of the 19 chapters which comprise the book are by psychologists, although some work by specialists in other fields is also included. Detailed chapters are devoted to a variety of adverse conditions which can exert stressful pressures: cancer, ischemic heart disease, HIV/AIDS, and other chronic illnesses. These, as physicians know only too well, bring their burdens of anxiety and depression, which worsen further the quality of life. There is detailed consideration of the need for social support and techniques for coping.

It is much more difficult to show the reverse process: the ability of stress to produce organic disease. What is clear is that emotional factors may play some part in the onset and course of many medical conditions. However, the most convincing evidence that stress may be a significant aetiological factor for a specific illness concerns the association between acute myocardial infarction and psychological variables. Some of the authors who contribute to this book casually include other conditions (such as essential hypertension) for which, on the basis of much less adequate evidence, emotional factors have been claimed to be important primary causes. This book does not always provide adequate critical assessments of the evidence which it presents: instead, the mission of the authors seems (with some encouraging exceptions) to be to accumulate everything which can be traced in the scientific literature in support of the

claimed aetiological relation, to add to their case. It would be unfair to liken the approach to that of the uncritical advocates of psychosomatic medicine between 1930 and 1950, who produced an immense, tendentious literature supporting the case for the alleged emotional origins of essential hypertension, rheumatoid arthritis, thyrotoxicosis, peptic ulcer, ulcerative colitis, neurodermatitis, and asthma. But it is unfortunate that some of the literature on stress reviewed in this expensive handbook has not been presented with more rigorous criticism.

The book offers few practical tips to occupational physicians who advise companies on personnel policies aimed at reducing the adverse effects of restructuring and "downsizing", without jeopardising economic objectives. Professional advisers are only too aware of the reality of stress in organisations which are undergoing such changes. Uncertainties about job security, workload, roles, and self esteem give rise to anxiety and depression, and today general practitioners increasingly certify that stress is the cause of the resulting sickness absence. Those to whom senior managers and personnel directors must answer are concerned above all with financial viability, but many are also responsive to practical, cost neutral proposals for preserving the morale of the workforce.

Although the handbook contains little direct practical guidance, some of the academic work which it reviews can nevertheless be interpreted in helpful terms for this purpose. An example will illustrate this. An employee's performance generally increases, up to a point, as pressure of work goes up: but a critical point is reached beyond which increasing pressure fails to boost output—and may damage performance irreversibly. Again, there is an engineering analogy: increasing tension in a metal sample produces reversible stretching until the elastic limit is exceeded, after which irreversible changes and breakage occur. In employees, the critical point differs from person to person. The changes underway in many companies have the effect of removing people whose critical point is too easily reached. But there are alternatives: for example it is now clear that, if people are allowed some control over how they do their jobs, they are less at risk than those upon whom pressures are imposed with little flexibility or empowerment.

G DIGGLE

The Pharmacological Basis of Therapeutics, 9th ed. By GOODMAN, GILMAN. (Pp 1905; price £65.00.) 1996. New York: McGraw Hill. ISBN 0-07-026266-7.

Goodman and Gilman (G and G) was described many years ago as the "Blue Bible of Pharmacology"—this edition is black but still the best textbook of pharmacology and therapeutics available. Occupational physicians wishing to understand toxicological and pharmacological principles and needing a reference source for information on drugs and chemicals, will find this edition an excellent addition to their libraries.

The editors acknowledge that this is the first edition not to be edited by a Goodman or a Gilman and have, sensibly, preserved the best features of earlier editions while adding many excellent new features. These include several new chapters (including one on gene therapy), synopses at the opening of

each chapter, and a prospectus setting out likely future advances at the end of each chapter. This latter innovation is very valuable: not only is G and G now up to date, but it also provides the information which you may need next year.

In reviewing this book I have looked closely at the very familiar group of chapters on the autonomic (ANS) and central nervous systems (CNS). This has been a chastening experience, especially with regard to the CNS. The group of chapters starts with an account of neurotransmission (the fold-out diagram of the ANS remains) which is splendidly up to date but which still includes adequate accounts of the historical development of the field. This has always been a feature of G and G and it is good to see that it has not been lost. The diagrams explaining neurotransmission have been improved and now involve a modest use of colour. This is helpful and attractive. Details of such esoteric subjects as structure of the "docking complex" for neurotransmitters (do you know about neurexin and syntaxin?) are rapidly assimilated from the excellent diagrams. As one would expect, subtypes of nicotinic and muscolinic receptors are discussed in detail. The referencing of this chapter is as up to date as one could hope in a book of this size: references from 1994 and one from 1898 are included.

The chapter on anticholinesterase (AChE) agents has been an old friend for 15 years. Palmer Taylor has taken over the authorship of this chapter from Koelle and has added a valuable series of diagrams illustrating the interaction between the AChE molecule and the anti-AChE molecule. A useful note on Alzheimer's disease and the possible value of anticholinesterase agents in its management has also been included. The bibliography of the chapter has been shortened and it is odd that Koelle's masterpiece (*Handbuche der Experimentellen Pharmakologie*, 1963) and Ballantyne and Marrs' more recent volume (in many ways the successor to Koelle's work) do not figure more prominently.

To other chapters: those in the treatment of myocardial ischaemia and hypertension seem uniformly excellent as is that on the management of asthma. The latter stresses asthma as a predominantly inflammatory disorder and provides a concise review of the inflammatory mediators which may be involved in its pathogenesis. The prospectus is brief, perhaps disappointingly so. As well as being a textbook of pharmacology, G and G has always been a textbook of toxicology. This edition maintains that tradition with a chapter on heavy metals and one on non-metallic environmental toxicants by Klaasen. The reviews, on a compound by compound basis, are short but the coverage is good and although the bibliography looks just a little dated (no Schwartz, Pope, or Dockery on particles), there are some references to works published in 1994. The book concludes with 79 pages of tables of pharmacokinetic data dealing with about 360 drugs. This is a unique source of information.

Goodman and Gilman is a large book and this review, although long, does not do it justice. That such a book can be priced at £65 is nothing short of amazing. No doctor, pharmacologist or toxicologist, or even medical student could spend £65 or many hours better than by buying and reading this book. For those who have entered the computer age there is even a version available on CD-Rom.

R L MAYNARD