evidence on combined oral contraceptives in which he focuses on one factor at a time, factors such as duration of use or use near the menopause, and provides tables which juxtapose the results from all the known case–control and cohort studies which address the importance of that factor. The third, by David Skegg, addresses the broader issue of how the possible excess risk of breast cancer resulting from pill use should be viewed in the context of other risks and benefits.

There are also informative appendices describing the evolving formulations of oral contraceptives and the limitations of animal models for elucidating the action of sex steroid hormones on humans.

The first half of the book is more disappointing. It attempts an overview not only of the epidemiology and public health issues but also of biological research. The Committee have had difficulty in structuring the presentation, perhaps because they were aiming at a wide audience. The style of writing is at times a bit annoyingly unscientific or banal: "About a dozen factors are at the core of what is—and is not—known". "It is always easier to record a case of disease than the fact that a disease did not occur".

A very large number of factors that may play a part in mediating the response of breast tissue to steroid hormones are mentioned, but I did not feel that the section on biology improved my general understanding of the subject or that I was left wiser about which lines of enquiry in so exciting a field should have the greatest priority. The book raises many questions but does not seem to provide a guiding light.

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News

Tumour Markers: A Personal Appraisal

A comprehensive review of the use of tumour markers in clinical practice and of recent research relating to the field was presented at the venue on 'Tumour Markers: Current Applications and Impact on Therapy' (Nice, 16–19 November 1991 *J Tumor Marker Oncol*, 1991, **6**, 1–143.), jointly organised by the Mediterranean Society of Tumour Marker Oncology (MESTMO) and the International Academy of Tumour Marker Oncology (IATMO). This conference recalled unsolved issues, but also highlighted new dilemmas.

Characterisation of tumour markers

Any progress in the study of proteins can impinge directly upon that of tumour markers. For instance, 'outlaw' oestrogen receptors (ER) with mutations have recently been identified in breast cancer. These could activate gene transcription and stimulate tumour growth in the absence of oestrogen (dominant positive) or prevent normal receptor activation by oestrogen and possibly inhibit cell growth (dominant negative) (W.L. McGuire, San Antonio). Since sequence differences influence 3D-conformations, some of these receptors may not be adequately assayed by classic radioligands nor by monoclonal antibodies that are raised against defined peptide sequences of the full-length normal receptor. Moreover, such observations could account for the different ligand affinities observed in earlier studies.

Standardisation and quality assurance

The notion that each antibody measures a different species as regards 3D-structure intensifies the existing challenge arising from varied assay methods and from markers from different companies with different units and cut-off levels. Diversity implies the need for standardisation vs. a chosen reference especially when government authorities plan to set proficiency tests for laboratories. A consensus was also reached on the need for participation in external quality assessment schemes as being the only way to evaluate a laboratory's performance over time and in relation to other institutions (M.K. Schwartz, New York).

One or more tumour markers?

Mutated oestrogen receptors in breast cancer may help to explain absence of correlation between receptor positivity and response to hormone treatment. An explanation has also been sought in the presence of independent factors implicated in cell growth. In about 65% of ovarian cancers, epidermal growth factor receptor (EGFR) overexpression is associated with a poor prognosis (R.C. Bast, Durham N.C.) but EGFR levels are liable to be inversely related to ER and thus constitute redundant information. Of the new markers under active study (HER-2/neu (*c-erb* B2) oncogene expression, Ki 67 antigen, PS 2, heat shock proteins, transforming growth factors, topoisomerase. . .), so far, only an aspartyl protease of lysosomes, cathepsin D, has proved to be an independent prognostic variable suitable for routine assay in breast cancer management (H. Rochefort, Montpellier).

The simultaneous measurement of osteocalcin for the presence of bone metastases in prostate cancer was recommended to improve the prognostic value of the proteolytic glycoprotein prostate-specific antigen (PSA), a more sensitive marker than orthophosphoric monoester phosphohydrolase prostatic acid phosphatase (PAP) (E.H. Cooper, Leeds) but, as the number of markers is increased, so does the difficulty in data analysis. Presently, the proportional hazard multivariate regression analysis of Cox is the norm. It establishes a hierarchy of importance in a series of variables chosen to explain a single end-point that is usually disease-free interval or survival. Using this method, the prognostic significance of the following criteria: primary

President MESTMO: A. Khalifa, Ain Shams Faculty of Medicine, Cairo, Egypt; Vice-President MESTMO: M. Namer, Centre Antoine Lacassagne, Nice, France; President IATMO: J.V. Klavins, Cornell University Medical College, New York, U.S.A.; and Vice-President IATMO: G.D. Birkmayer, Laboratory for BIO-Analytik, Vienna, Austria.

tumour size, histological grade, node involvement, steroid receptor and total cathepsin D content, levels of serum CEA and of polymorphic epithelial mucin as measured by three antibodies (CA 15:3, MCA, and BCM), chosen from a much longer and much debated list (CA M26, CA M29, CA 549, EMCA. . .), was evaluated in breast cancer patients with metastatic lesions situated in different loci (lung, bone and/or liver) (M. Namer, Nice).

Tumour markers: the signal for treatment?

The attitude to be adopted when tumour marker values increase in a patient in remission with no clinical manifestations of relapse is a major issue. Should no effort be spared to detect metastases and/or should the patient immediately receive treatment? In an ongoing prospective study in women with breast cancer in remission (W. Jäger, Erlangen), serum CEA and CA:53 are being measured monthly on a voluntary basis. When an increase is confirmed, the patient is invited to partake in a randomised trial and receives either placebo or medroxyprogesterone acetate. An intermediary analysis has revealed a definite trend in favour of treatment.

Descriptions of patient populations

Studies like the above have to be validated. On the other hand, much of the effort expended in reproducing results on few variables in small studies could be usefully diverted towards a more exhaustive analysis of why some patients respond and others do not. To avoid repetition of trials, there is a need for a better description of patient populations. Oestrogen and progesterone receptors have been assayed for over 20 years in breast tissue in order to assess hormone dependence but the need to seriously consider menopausal status and to define appropriate cut-off levels for pre- and post-menopause and for each receptor in order to interpret survival and therapy results is only being emphasised now (S.M. Thorpe, Copenhagen). The analysis of the possible covariations among suspected markers and other variables in patient records (age, race, blood group, sex, menopausal status, plasma hormone levels, genetic and environmental factors. . .) has received little or no attention. A clinician might appreciate a descriptive map of his patient population so that if a certain patient responds well to a treatment, the chances that his nearest neighbour with the closest profile on the map will also respond are high. This would be a welcome shift from the evaluation of statistical risk towards individual risk.

Statistics was a focal point of several presentations. W.L. McGuire (San Antonio) emphasised the chance of a spurious result when attempting to relate the outcome of mastectomy to the time of the menstrual cycle and concluded with perspectives of novel analytical methods such as tree decision and neural net analyses. In a poster by E. Coulomb and P.M. Martin (Marseilles) on tumour sensitivity to anthracyclins, subpopulations of breast epithelial cells in different cell cycle phases were identified by a discriminant analysis. Discriminant analysis was also used by F. Salvatore (Naples) to show which combination of three out of five serum isoenzymes improve clinical discrimination (up to 95%) between cirrhosis and liver neoplasia and to deduce that each of these markers represents a different aspect of biological activity. The time may now be ripe to reconsider multivariate methods such as factorial analyses and automatic classification procedures used in other disciplines (phylogeny, taxonomy, social sciences) in order to establish relationships among tumour markers, among patients, and between tumour markers and patients.

Genetic markers

Genetic markers of predisposition to cancer are playing an increasingly important role in patient description. The list of tumour suppressor genes is expanding fast (p53 gene; Ca^{2+}-independent cell–cell adhesion molecules; Ca^{2+}-dependent cadherins in liver, prostate and breast cancer; the wwTi gene, NF1; adenoma poly c (apc) genes. . .) and will probably override that of protooncogenes in determining tumour phenotype and as prognosis factors (R. Monier, Villejuif).

Mutation of p53 is common in many cancers (e.g. lung, breast. . .) and in the familial Li-Fraumeni syndrome. Over 100 point mutations are known. Since wild p53 has a very short half-life, only the more stable mutated protein can be detected immunohistochemically. In D.M. Barnes' (London) study of 102 breast cancers, 36% showed strong p53 staining, 42% weak staining with a close association with histological grade, and 22% were unstained. In non-metastatic human colorectal cancers, p53 was detected by flow cytometry using a panel of three monoclonal antibodies in 69% of cases (Y. Remvikos, Paris). Actuarial survival was 57% at 3 years for p53-positive cases compared with 95% for p53-negative cases.

B. Dutrillaux (Paris) estimated the ratio of abnormal vs. total chromosomes in each of 110 tumours and showed that the reduction in chromosome number, also reflected in a loss in DNA content, was strongly correlated with increased chromosome rearrangement and possibly with DNA methylation which could prevent recombination of partially homologous DNA regions. Interestingly, the rate of rearrangement was inversely correlated with steroid hormone receptor expression and with S-phase both in paradiploid and hyperploid tumours, and also with EGFR in paradiploid tumours.

Tumour markers and treatment: point and counterpoint

Encouraging results have been obtained during a Phase I pharmacoclinical study on the administration of various doses of a monoclonal antibody for EGFR, a receptor overexpressed in glioblastoma (H. Magdelenat, Paris). In breast cancer, ER is both marker and target. However, the current practice of measuring ER with a single radioligand or antibody with a view to a single standard treatment (usually the antioestrogen tamoxifen) may be too single-minded and greater therapeutic efficiency may in future be achieved by the development of new protein types, e.g. antisense proteins, that, as outlined by R.K. Busch (Houston) for p120, can inhibit cell growth.

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The European School of Oncology

10th ANNIVERSARY SEMINARS

15th - 16th October, 1992

Milan, Italy

Bioethics in Oncology

Chairpersons: J. Holland (US), M. Slevin (GB)

Faculty: Aaronson (NL), Cazzullo (IT)), Fiorentino (IT), Koinuma (JP), Lederberg (US), McDonnell (KE), Olweny (US), Rothman (US), Ventafridda (IT), Veronesi (IT), Weil (FR)

Truth telling in the Western European context; Changing patterns in Japan; Medicine and government; Ethical issues in developing countries; Euthanasia and other media favorites; Terminal care and ethics in the developing countries; Planning a global research and educational agenda in bioethics.

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Chemoprevention of Cancer

Chairpersons: M. Sporn (US), P. Boyle (IT)

Faculty: Jordan (US), Cuzick (GB), Ki Hong (US), McVie (GB), Moon (US), Powles (GB), Schroeder (NL), Veronesi (IT), Walker (US), Willett (US)

Tamoxifen and prevention of breast cancer; Ongoing studies on tamoxifen in the US, the UK and Italy; Retinoids and cancer prevention; The Milan cancer chemoprevention programme; EUROSCAN; Prevention of prostate cancer; Methodology.

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Immunodiagnosis of Tumours

Chairperson: S. von Kleist (DE)

Faculty: Bradwell (GB), Buraggi (IT), Denk (AT), Gion (IT), Hertel (DE), Hor (DE), Noujaim (CA), Schwartz (US), Wittekind (DE)

In vitro procedures for immunodiagnosis; New serological marker substances; Immunohistology - a new diagnostical dimension; *In vivo* technologies for immunodiagnosis; Radioimmunodetection as a model for biologically targeted radiotherapy.

Tobacco Carcinogenesis and Control

Chairpersons: P. Boyle (IT), M. Peckham (GB), W. Zatonski (PL), H. Zur Hausen (DE)

Faculty: Bartsch (FR), La Vecchia (IT), Martin-Moreno (ES), Maynard (GB), Schwab (DE), Walker (US), Wood (GB)

The epidemiological evidence of cigars, pipes and cigarette smoking and risk of cancer; Differences in the effect of black and blond tobacco on cancer risk; Chemical carcinogenesis and mechanisms; Preventive strategies and their efficacy; Introduction of "European Oncologists Against Tobacco".

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Cutaneous Melanoma

Chairperson: N. Cascinelli (IT)

Faculty: Anichini (IT), Bajetta (IT), Belli (IT), Cook (GB), Coulie (NL), Giannotti (IT), Illeni (IT), Kirkwood (US), Mackie (GB), Mihm (US), Natali (IT), Parmiani (IT), Rilke (IT), Rovini (IT), Santinami (IT), Soyer (AT), Vaglini (IT), Zurrida (IT)

Diagnosis of cutaneous melanoma; Utility and limits of prevention campaigns in melanoma; Therapeutic programming at the Istituto Nazionale Tumori (Milan); Immunological research.

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Prostate Cancer 2000

Chairpersons: L. Denis (BE), G. Murphy (US)

Faculty: Bagshaw (US), Boyle (IT), Coffey (US), Di Silverio (IT), Griffiths (GB), Pagano (IT), Scher (US), Schroeder (NL), Walsh (US)

Epidemiology of prostate cancer; Prevention; Biology of prostate cancer; Endocrinology of prostate cancer; Radical prostatectomy; Radiotherapy; Endocrine therapy; Chemotherapy; Future considerations.

For further information contact:
The Secretariat, European School of Oncology,
Via Venezian 18, 20133 Milan, Italy
Tel: (+ 39 2)70635923-2364283 Fax: (+ 39 2)2664662

Cancer of the Testis

The 3rd international workshop on carcinoma *in situ* and cancer of the testis will be held on 1–4 November, 1992, in Copenhagen. For details, contact Workshop Secretariat, c/o Professor Niels E. Skakkebaek, University Department of Growth and Reproduction, Section 5064, Rigshospitalet, 9 Blegdamsvej, DK—2100 Copenhagen, Denmark. Tel: 3545 5085, Fax: 3139 9054.

New Chemotherapies

The 10th Chemotherapy Foundation Symposium on innovative cancer chemotherapy will be held in New York City on 11–13 November 1992. Further information can be obtained from Jaclyn Silverman, Division of Medical Oncology, Box 1178, Mount Sinai School of Medicine, 1 Gustave Levy Place, New York, New York 10029, U.S.A. Tel: 212 241 6772 and 212 369 5440.

Transrectal Ultrasound and Prostate Cancer

The seventh international symposium on transrectal ultrasound in the diagnosis and management of benign prostatic hypertrophy and prostate cancer will be held on 11–13 September 1992, in Chicago. Further information can be obtained from Diversified Conference Management Inc., P.O. Box 2508, Ann Arbor, MI 48106, USA. Tel: (1) 313 6652535.

Breast Cancer Symposium

The 215th annual San Antonio breast cancer symposium will take place on 9–10 December 1992, in San Antonio. This meeting is sponsored by the Cancer Therapy and Research Center, the American Cancer Society Texas Division and the National Cancer Institute with the University of Texas Health Science Center at San Antonio. Further details can be obtained from Ms Lois Dunnington, Symposium Coordinator. Tel: (1) 512 5674745, Fax: (1) 512 6175221 or (1) 512 6929823.

Supportive Care in Cancer

The fourth international symposium on supportive care in cancer will be held in St Gallen, Switzerland, on 24–27 February 1993. The abstract deadline is 15 November 1992. For more details, contact Mrs Beatrice Nair, Conference Manager "SUP-93", c/o Professor H.J. Senn, Department of Medicine C (Oncology), Kantonsspital, CH-9007 St Gallen, Switzerland. Tel: (41) 71 261097, Fax: (41) 71 256805.

Neutron Capture Therapy

The fifth international symposium on neutron capture therapy will be held in Columbus, OH on 13–17 September, 1992. Further details can be obtained from the Secretariat, Fifth International Symposium on Neutron Capture Therapy, Parks Hall, 500 West 12th Avenue, Columbus, OH 43210-1291, USA. Fax: 614 292 2435.

Macrophage Biology

A European conference on basic and clinical aspects of macrophage biology will take place in Regensburg, Germany, on 20–22 September, 1992. For further information, contact Professor Reinhard Andreesen, Klinik and Poliklinik fur Innere Medizin I, Universitat Regensburg, Franz-Josef-Str Allee 11, D-8400 Regensburg, FRG. Tel: 941 9447110, Fax: 941 9447111.

Immunotherapy

The New York Academy of Sciences is sponsoring a meeting on the specific immunotherapy of cancer with vaccines in Washington, DC on 21–24 January, 1993. More details can be obtained from the Conference Department, New York Academy of Sciences, 2 East 63rd Street, New York, NY 10021, USA. Tel: +1 212 838 0230, Fax: 212 888 2894.

Oncology Conference

The third European Winter Oncology Conference will take place in Meribel, France, on 23–29 January 1993. For further details, contact Mrs L. Minnen, EWOC-3 Meeting Secretariat, Division of Oncology, U.H. St. Rafaël, Kapucijnenvoer 35, 3000 Leuven, Belgium. Tel: +32 16 212230, Fax: 16 212228.

Carotenoids

The New York Academy of Sciences is sponsoring a meeting on carotenoids in human health in San Diego on 6–9 February 1993. More details can be obtained from the Conference Department, New York Academy of Sciences, 2 East 63rd Street, New York, NY 10021, USA. Tel: +1 212 838 0230, Fax: 212 888 2894.

Adjuvant Therapy

The Arizona Cancer Center is sponsoring the seventh international conference on adjuvant therapy in cancer in Tucson, AZ on 10–13 March, 1993. For further information, contact Nancy Rzewuski, Conference Coordinator, Arizona Cancer Center, University of Arizona College of Medicine, Room 2993, 1515 N. Campbell Avenue, Tucson, AZ 85724, USA. Tel: 602 626 2276, Fax: 602 626 2284.

Melanoma

The third international conference on melanoma is to be held in Venice from 31 March to 3 April, 1993. Further details can be obtained from Dr Mario Santinami, Istituto Nazionale Tumori, Via G Venezian 1, 20133 Milan, Italy. Tel: +39 2 2663992/26680626, Fax: 26680636.