G. Mathé

Cancer Active Immunotherapy

Immunoprophylaxis and Immunorestoration

An Introduction

G. Mathé

Cancer Active Immunotherapy

Immunoprophylaxis and Immunorestoration

An Introduction

With 123 Figures

Springer-Verlag
Berlin · Heidelberg · New York 1976

GEORGES MATHÉ, MD, Professor of Oncology,
University of Paris Sud,
Institut de Cancérologie et d'Immunogénétique,
Unité Fred Siguier, Hopital Paul Brousse,
and Division of Hematology, Institut Gustave Roussy,
Villejuif, France

Sponsored by the Swiss League against Cancer

ISBN 3-540-07601-8 Springer-Verlag Berlin·Heidelberg·New York
ISBN 0-387-07601-8 Springer-Verlag New York·Heidelberg·Berlin

Library of Congress Cataloging in Publication Data. Mathé, Georges, 1922— Cancer active immunotherapy, immunoprophylaxis, and immunorestoration.
(Recent results in cancer research; 55.) Bibliography: p.
1. Immunotherapy. 2. Cancer-Immunological aspects. I. Title. II. Series.
[DNLM: 1. Neoplasms-Prevention and control. 2. Neoplasms-Therapy. 3. Immunotherapy. 4. Biological products-Therapeutic use. 5. Adjuvants, Immunologic-Therapeutic use. W1 RE106P v. 55/QZ266 M426i.] RC261.R35 vol. 55
[RC271.I45] 616.9'94'008s. [616.9'94'079] 76-33.

Typesetting, printing and binding:
Konrad Triltsch, Graphischer Betrieb, 87 Würzburg, Germany.

Preface

I would like to thank all my co-workers who have collaborated with me, from 1963 until now, in biological and clinical research in the field of cancer active immunotherapy, of its immunoprevention and immunorestoration. They will often be quoted in this book.
I am particularly grateful to those who have helped me to write it by reviewing some chapters: D. Belpomme, J. F. Doré, Irene Florentin, A. Goutner, I. J. Hiu, R. Huchet and Marie-Christine Simmler.
I also thank Nicole Vriz, Marie-Claude Schneider, Fenella Riseley and M. Juvet for their willing and efficient co-operation in the preperation of the manuscript.
I am finally grateful to all authors of books or articles who authorized me to reproduce their figures or tables.

Paris, April 1976 G. Mathé

Contents

Chapter 1. Introduction and Definitions 1

Chapter 2. Biological Basis: Tumour Associated Antigens, the Immune Machinery and Its Behaviour Concerning Cancer Cells 5

2.1. Tumour-Associated Antigens 5
2.2. The Immune Machinery 19
2.2.1. Humoral Mediated Immunity and Cell Mediated Immunity 19
2.2.2. T- and B-Lymphocyte and Monocyte Differentiation 22
2.2.3. T-Lymphocyte Functions 25
2.2.4. B-Lymphocyte Functions 30
2.2.5. Macrophage Functions 31
2.2.6. K-Cell Function 32
2.3. The Immune Machinery and Cancer Cells 33
2.3.1. Mechanisms Involved in Tumour Cell Rejection 33
2.3.1.1. In vivo Evidence for Tumour Immunity 33
2.3.1.2. In vitro Assays for Cell Mediated Immunity 36
2.3.1.3. Role of T-Lymphocytes in Tumour Rejection 36
2.3.1.4. Role of Antibody in Tumour Cell Rejection 38
2.3.1.5. Role of K-Cells 39
2.3.1.6. Role of Macrophages 41
2.3.2. Escape Mechanisms to Tumour Destruction 45
2.3.2.1. Escape Mechanisms Prior to Tumour Establishment 45
2.3.2.2. Escape Mechanisms after Tumour Establishment 49
2.3.2.2.1. Role of Serum Blocking Factors 50
2.3.2.2.2. Role of Suppressor Cells 54
2.3.2.2.3. Role of the Tumour Itself 55
2.3.3. The Immune Balance 58

Chapter 3. Systemic Active Immunotherapy 76

3.1. Experimental 76
3.1.1. Leukaemias 76

3.1.1.1. Active Immunotherapy on Limited Tumour Cell Populations 76
3.1.1.2. Type of Action: The Plateau of Tumour Growth Phenomenon 77
3.1.1.3. Comparison of the Use of Sterilized Tumour Cells, a Systemic Immunity Adjuvant (BCG), or a Combination of Both 78
3.1.1.4. Active Immunotherapy after Cell Reduction by Chemotherapy 80
3.1.1.5. Immunotherapy and Immunological Parameters 82
3.1.1.6. Active Immunotherapy of Perceptible Voluminous Leukaemia 84
3.1.2. Solid Tumors 85
3.1.2.1. Active Immunotherapy on Limited Tumour Cell Population 85
3.1.2.2. Active Immunotherapy after Cell Reduction by Surgery and/or Radiotherapy and/or Chemo- or Hormonotherapy 85
3.1.2.3. Active Systemic Immunotherapy of Perceptible Voluminous Solid Tumours 88
3.1.2.4. Immunotherapy of Metastasis 89
3.1.3. Problems Common to Leukaemias and Solid Tumours 90
3.1.3.1. The Myth of Immunological Tolerance in the Case of Tumours Associated with Vertically Transmitted Spontaneous Virus 90
3.1.3.2. Immunotherapy and Chemotherapy Interspersed 91
3.1.3.3. Negative Results 95
3.1.3.4. The Possibility of Neoplasia Growth Enhancement 95
3.2. Clinical 96
3.2.1. Leukaemias and Hematosarcomas 96
3.2.1.1. Residual Imperceptible Disease 96
3.2.1.1.1. Acute Lymphoid Leukaemia 96
3.2.1.1.2. Acute Myeloid Leukaemia 114
3.2.1.1.3. Blastic Crisis of Chronic Myeloid Leukaemia 121
3.2.1.1.4. Lymphosarcomas 121
3.2.1.1.5. Hodgkin's Disease 123
3.2.1.2. Treatment of Perceptible Disease 123
3.2.1.2.1. Acute Lymphoid Leukaemia 123
3.2.2. Solid Tumours 125
3.2.2.1. Treatment of Residual Imperceptible Disease 125
3.2.2.1.1. Special Case of Placental Choriocarcinoma 125
3.2.2.1.2. Melanoma 126
3.2.2.1.3. Bronchus Cancer 129
3.2.2.1.4. Mammary Carcinoma 129
3.2.2.1.5. Osteosarcoma 129
3.2.2.2. Treatment of Perceptible Disease 130
3.2.2.2.1. Melanoma 130
3.2.2.2.2. Bronchus Cancer 131

3.2.2.2.3. Head and Neck Tumours 132
3.2.2.2.4. Gynaecological Cancers 132
3.2.2.2.5. Brain Tumours 132
3.2.2.2.6. Various Tumours 132
3.2.3. Problems Common to Leukaemia and Solid Tumours 132
3.2.3.1. Immunotherapy and Chemotherapy Interspersed 132
3.2.3.2. Negative Results 133
3.2.3.3. Possibility of Neoplasia Growth Enhancement 133

Chapter 4. Cancer Local Active Immunotherapy 143

4.1. Experimental 143
4.1.1. BCG and Other Mycobacteria 143
4.1.2. Corynebacteria and Other Bacterias 144
4.1.3. Other Agents 145
4.1.4. Failures and Factors and Conditions of Efficacy 145
4.1.5. Possibility of Neoplasia Growth Enhancement 147
4.2. Clinical 147
4.2.1. BCG 147
4.2.2. Other Agents 147
4.2.3. Failures, Factors and Conditions of Efficacy 149
4.2.4. Possibility of Neoplasia Growth Enhancement 150

Chapter 5. Towards Immunoprophylaxis 153

5.1. Experimental 153
5.1.1. Grafted Tumours 153
5.1.1.1. Use of Neoplastic Cells 153
5.1.1.2. Use of Systemic Immunity Adjuvants 154
5.1.1.3. Combination of an Adjuvant and of Tumour Cells 157
5.1.2. Carcinogen Induced and Spontaneous Tumours 157
5.1.2.1. Virus Induced Tumours 157
5.1.2.1.1. Use of Tumour Cells or Viruses 157
5.1.2.1.2. Use of Systemic Immunity Adjuvants 158
5.1.2.1.3. Use of a Combination of an Adjuvant and of Tumour Cells or Viruses 158
5.1.2.2. Chemically Induced Tumours 159
5.1.2.2.1. Use of Cells 159
5.1.2.2.2. Use of Systemic Immunity Adjuvants 159
5.1.2.3. Does Immunoprophylaxis Work before Carcinogenes is Established? 159
5.1.2.4. Failures 161

5.1.2.5. Possibility of Neoplasia Growth Enhancement 161
5.1.2.5.1. Grafted Tumours 161
5.1.2.5.2. Induced Tumours 162
5.2. Clinical 162
5.2.1. Prophylaxis of Blastic Crisis of Chronic Myeloid Leukaemia 162
5.2.2. Prophylaxis of Childhood Leukaemia by BCG Vaccination 163

Chapter 6. Towards Immune Restoration 169

6.1. Immunodeficiency Associated with Cancer, and Cancer Risk in Immunodeficiency Subjects 169
6.1.1. Experimental 170
6.1.1.1. Animals with Cancer 170
6.1.1.2. Cancer Risk in Immunodeficient Animals 173
6.1.2. Clinical 173
6.1.2.1. Cancer Patients 173
6.1.2.1.1. Immunodeficiency Due to Treatments 173
6.1.2.1.2. Immunodeficiency Due to/or Associated with Cancer 175
6.1.2.2. Immunodeficiency Diseases or Syndromes with High Cancer Risk 188
6.2. Attempts at Immunorestoration 192
6.2.1. Experimental 192
6.2.1.1. Use of Thymic Lymphocyte-Stimulating Factor (or Thymosin) 192
6.2.1.2. Use of Adjuvants 193
6.2.2. Clinical 194
6.2.2.1. Transfer Factor 194
6.2.2.2. Thymus Lymphocyte Stimulating Factor (or Thymosin) 195
6.2.2.3. Adjuvants 196
6.2.2.4. Immune "Restoration" by Proteolysis 200
6.2.2.5. Immunorestoration by Surgery 200
6.2.2.6. Immunorestoration by Cancer Chemotherapy 200
6.2.2.7. Combined Methods 201

Chapter 7. Developmental Pharmacology 208

7.1. Systemic Specific Active Immunotherapy or Immunoprophylaxis 208
7.1.1. Tumour Cells and/or Antigens 208
7.1.1.1. Should Antigenicity be Restricted to Tumour-Associated Antigens or Not? 208
7.1.1.2. Allogeneic Versus Autologous Materials. Tumour Type Cells for Treated Tumour Types 209
7.1.1.3. Antigenicity and/or Immunogenicity 210
7.1.1.5. Division-Sterilized Cells 211

7.1.1.6. Cryopreserved Cells 213
7.1.1.7. Pooled Cells 214
7.1.1.8. Subpopulations of Cells 214
7.1.1.9. Living Versus Killed Cells 215
7.1.2.0. Modified Cells 215
7.1.2.1. Cultured Cells 220
7.1.2.2. Modified Normal Cells 221
7.1.2.3. Hybridized Cells 222
7.1.2.4. Tumour-Associated Antigen Preparations 222
7.1.2. Dose Factor 224
7.1.3. Sites of Administration 225
7.1.4. Should Cells or Antigens be Mixed with the Adjuvant? 225
7.2. Systemic Non-Specific Active Immunointervention 227
7.2.1. Systemic Immunity Adjuvants 227
7.2.1.1. The Innumerable Adjuvants in the Literature 227
7.2.1.2. Experimental Screening and Pharmacology 227
7.2.1.2.1. The ICIG-EORTC Experimental Screening for Systemic Immunity Adjuvants 227
7.2.1.2.2. BCG Preparations and Presentation 241
7.2.1.2.3. Extracts of BCG and Other Mycobacterias 249
7.2.1.2.4. Corynebacteria Preparations 254
7.2.1.2.5. Polynucleotides 256
7.2.1.2.6. Other Agents 257
7.2.1.2.7. Experimental Pharmacology 257
7.2.1.3. Clinical Screening and Pharmacology 266
7.2.1.3.1. The ICIG-EORTC Clinical Screening for Systemic Immunity Adjuvants or Immunorestorators 267
7.2.1.3.2. Clinical Pharmacology 268
7.2.1.3.2.1. BCG Preparations 268
7.2.1.3.2.2. Mycobacteria Extracts 273
7.2.1.3.2.3. Corynebacteria 273
7.2.1.3.2.4. Polynucleotides 274
7.2.1.3.2.5. Other Agents 274
7.2.1.3.2.6. Combinations of Several Adjuvants 274
7.2.2. Hormones 275
7.2.2.1. Experimental 275
7.2.2.1.1. Oestrogens 275
7.2.2.1.2. Thymosin 275
7.2.2.2. Clinical 276
7.2.2.2.1. Oestrogens 276
7.2.2.2.2. Thymosin 276
7.3. Local Immunotherapy 276
7.3.1. Experimental Pharmacology 276
7.3.1.1. BCG 276
7.3.1.2. Extracts from Mycobacteria 277
7.3.1.3. Corynbacteria 278
7.3.1.4. Bordetella Pertussis 278
7.3.1.5. Other Materials 278
7.3.1.6. Mixtures 279
7.3.2. Clinical Pharmacology 279

7.3.2.1. BCG 279
7.3.2.2. Other Materials 280

Chapter 8. Toxicology and Adverse Effects 295

8.1. Systemic Active Immunotherapy 295
8.1.1. Experimental 295
8.1.1.1. Specific 295
8.1.1.2. Systemic Immunity Adjuvants 295
8.1.1.2.1. BCG 295
8.1.1.2.2. Mycobacteria Preparations 302
8.1.1.2.3. Corynebacteria and Other Micro-Organisms 302
8.1.1.2.4. Polynucleotides, Lentinan, Tetramisole, Vitamins 302
8.1.1.3. Miscellaneous 302
8.1.2. Clinical 302
8.1.2.1. Specific 302
8.1.2.2. Systemic Immunity Adjuvants 308
8.1.2.2.1. BCG 308
8.1.2.2.2. Mycobacterial Extracts 313
8.1.2.2.3. Corynebacteria 313
8.1.2.2.4. Bordetella Pertussis and Brucella Abortus 314
8.1.2.2.5. Polynucleotides 314
8.1.2.2.6. Other Agents 314
8.1.2.2.7. Combinations of Several Adjuvants 316
8.1.2.3. Hormones 316
8.1.2.4. Other Means 316
8.2. Local Active Immunotherapy 316
8.2.1. Experimental 316
8.2.2. Clinical 317

Chapter 9. Mechanisms of Favourable and Adverse Effects and of Failures 320

9.1. Systemic Immuno-Intervention 320
9.1.1. Specific Stimulus 320
9.1.2. Non-Specific 320
9.1.2.1. Adjuvants 320
9.1.2.1.1. Historical Adjuvants 320
9.1.2.1.2. Systemic Action of Adjuvants 321
9.1.2.1.3. Classification of Adjuvants According to Their Main Target Cells 336
9.1.2.1.4. Particular Study of Adjuvants Already Used in Man 339
9.1.2.1.4.1. BCG 339
9.1.2.1.4.2. Corynebacteria 342
9.1.2.1.4.3. Polynucleotides and Other Adjuvants 344
9.1.2.2. Hormones 345
9.1.3. Failures and Adverse Effects 345
9.1.3.1. Immune Inefficiency of Cancer Subjects 347

9.1.3.2. Possible Immunodepressive Effect of Adjuvants 347
9.1.3.3. Antigenic Competition 348
9.1.3.4. Immunological Enhancement 349
9.1.3.5. Tumour Volume and Blocking Humoral Factors 349
9.1.3.6. Anatomic Sites of Tumours 351
9.1.3.7. Lack of Antigenicity and/or Immunogenicity of the Tumours 351
9.1.3.8. Secondary Resistance to Immunotherapy 351
9.2. Local Immunotherapy 352

Chapter 10. Conclusion: Immunotherapy and Immunorestoration Today in the Strategy of Cancer Treatment; Their Perspectives and that of Immunoprophylaxis 364

10.1. Evaluation of the Immune Status of the Patient 365
10.2. Attempts at Immunorestoration in Case of Immunodepression 365
10.2.1. General Immunity 365
10.2.2. General Immunity and Sensitivity to Adjuvant(s) or Antigen(s) to be Used for Local Immunotherapy 366
10.3. The Patient is an Immunoresponder (Without or After Immunorestoration) 367
10.3.1. Residual Imperceptible Disease 367
10.3.2. Perceptible Tumours Not Curable by Surgery Radiotherapy or Chemotherapy 371
10.3.2.1. Indications for Local Immunotherapy 371
10.3.2.2. Indications for Systemic Immunotherapy 371
10.3.2.3. Combinations of Several Types of Immunotherapy 374
10.3.3. Surgery, Radiotherapy, Chemotherapy or Combination Curable Tumours 374
10.4. Immunoprophylaxis of Cancer 375

Chapter 11. Appendix: Towards Monitoring the Immunological Status and Its Modification Induced by Immunotherapy, Immunorestoration or Immunoprophylaxis 381

11.1. Exploration of General Responses 382
11.2. Attempts at Evaluating Responses to Tumour-Associated Antigens 390

Subject Index 403

Chapter 1
Introduction and Definitions

For decades, oncologists have seen many cancers locally eradicated by surgery or radiotherapy, which relapse in the form of one or more metastases, in site(s) distant from the primary one, and possibly recurring a long time after primary treatment. The fact that these metastases were not detectable before and after treatment means that surgeons and radiotherapists often leave a few malignant cells in a patient who has been locally well treated. Systematic complementary chemotherapy in such cases has recently been claimed to be an excellent means of preventing relapses (E.O.R.T.C., Radiochemoth. Group, 1972; JAFFE *et al.*, 1974; BERLIN, 1974). However, it has, in the past, been generally disappointing (MATHÉ and KENIS, 1975).

The same reason may explain its failure to cure patients with perceptible disseminated neoplasias, with the exception of certain leukaemias, haematosarcomas and exceptional solid tumours such as placental choriocarcinoma (MATHÉ and KENIS, 1975). The contrast between the rare incidence of cure and the high frequency of complete regressions or remissions, which mean retrogression of the population of residual tumour cells to a number which is imperceptible, is explained by the fact that chemotherapy obeys first order kinetics (SKIPPER *et al.*, 1964, 1965, 1967).

If this therapy always leaves a few cells, and if it nevertheless cures some patients, it is reasonable to wonder if the last cells, in the case of a cure, are not killed by immune reactions. Three questions arise:

a) Are immune reactions able to kill tumour cells? Experimentally, it has been known since the beginning of this century (LOEB, 1901; JENSEN, 1903) that grafts of incompatible tumours are rejected, and it was when he was studying transplantation of neoplasias to hosts of different genetic constitution, that SNELL (1953) determined the immunogenetics laws valuable for all tissues and/or organs.

Clinically, it was impossible not to correlate the fact that choriocarcinoma was the first human cancer to be cured by (not even intensive) chemotherapy, and its semi-allogenic relationship with its carrier. In the serum of the (female) patients, antibodies were demonstrated against the tissues of their respective husbands (MATHÉ *et al.*, 1964).

b) Are tumours, immunogenetically identical to their hosts, recognizable by their immunological machinery and sensitive to it? In other words, do cancer cells carry special antigens?

The answer is yes. Since FOLEY (1953) gave the first demonstration that murine tumours may be rejected by isogeneic hosts, a thousand papers have been devoted to "tumour-associated antigens" of experimental and human neoplasias (KOLDOVSKI, 1969).

c) Hence, if tumour cells are recognized by the immune machinery and sensitive to it, the third question arises: can we manipulate the latter in order to make it kill more cancer cells than it does naturally? The answer is yes.

Since 1955, in animal and in man (THOMPSON and MATHÉ, 1972), the reactions against leukaemias of incompatible grafted (with bone marrow) or transfused lymphocytes have been used, and this form of treatment has been called *adoptive immunotherapy*.

In the author's laboratory, MOTTA (1971) treated experimental leukaemias with manipulated sera from animals immunized with cells of these tumours *(passive immunotherapy)*.

After 1963, we were tempted to increase the number of tumour cells that a subject can destroy with its own immune machinery, and this manipulation was called *active immunotherapy)* (MATHÉ, 1968; MATHÉ, 1971): for this purpose the author used the administration of (sterilized) tumour cells, isogeneic to the neoplasia to be treated, or extract(s) containing their tumour-associated antigen(s) (MARTYRE, 1976) *(specific immunotherapy)* and/or agents known to be able to potentiate, in some conditions, the immune responses. In fact, they may modulate them in different ways (MATHÉ, 1973), hence the traditional name of *immunity "adjuvants"* that we have kept for these agents which are legion. The name of *nonspecific immunotherapy* is retained for their exclusive use.

Active immunotherapy has also to be divided into two categories according to the presentation of the disease to be treated: when there is a nonaccessible tumour, specially in the case of imperceptible residual neoplasia, only the *systemic* type can be applied.

When, on the other hand, a tumour is accessible to the injection of adjuvant(s), such an injection is recommended by some and this form of immunotherapy is called *local* (MORTON *et al.*, 1970).

The results obtained with cancer immunotherapy are inducing research on *immunorestoration* of immunodepressed cancer patients (SIMMLER *et al.*, 1976) and on tumour *immunoprophylaxis*.

Though there is apparently much less work devoted to the latter question than to immunotherapy, it should be remembered that adjuvants called at that time "stimulants of the reticuloendothelial system" (OLD *et al.*, 1961) were applied for the prevention of experimental grafted tumours particularly by HALPERN *et al.*, (1959), after DUBOS and SCHAEDLER (1957) had shown that they could prevent experimental infections.

References

BERLIN, N.I. (Ed.): A report to the profession from Breast Cancer Task Force, 30th September 1974. Bethesda: Department of Health Education and Welfare U.S.A.

DUBOS, R.J., SCHAEDLER, R.W.: J. Exp. Med. 106, 703 (1957).

European Organization for Research on the Treatment of Cancer (EORTC). Radiotherapy-chemotherapy Cooperative Group. Europ. J. Cancer 8, 353 (1972).

FOLEY, E.J.: Cancer Res. 13, 835 (1953).

HALPERN, B., BIOZZI, G., STIFFEL, C., MOUTON, D.: C.R. Soc. Biol. Paris 153, 919 (1959).

JAFFE, N., FREI, E. III, TRAGGIS, D., BISHOP, Y.: New England J. Med. 291, 994 (1974).

JENSEN, C.O.: Zentralbl. Bakt. 1 Abt. 34, 28, 122 (1903).

KOLDOVSKI, P.: Tumor specific transplantation antigen. 1 vol. Berlin-Heidelberg-New York: Springer-Verlag 1969.

LOEB, L.: J. Med. Res. 6, 28 (1901).

MARTYRE, M.C.: Biomedicine in press (1976).

MATHÉ, G.: Rev. Fr. Et. Clin. Biol. 13, 881 (1968).

MATHÉ, G.: Adv. Cancer Res. 14, 1 (1971).

MATHÉ, G.: p. 305 in "Immunopotentiation" (Ciba Foundation Symposium 18). 1 vol., Amsterdam: Elsevier Excerpta Medica 1973.

MATHÉ, G., DAUSSET, J., HERVET, E., AMIEL, J.L., COLOMBANI, J., BRULE, G.: J. Nat. Cancer Inst. 33, 193 (1964).

MATHÉ, G., KENIS, Y.: La chimiothérapie des cancers (leucémies, hématosarcomes et tumeurs solides). 3rd ed., Paris: Expansion Scientifique 1975.

MORTON, D.L., EILBER, F.R., JOSEPH, W.L., WOOD, W.C., TRAHAN, E., KETCHAM, A.S.: Ann. Surg. 172, 740 (1970).

MOTTA, R.: Adv. Cancer Res. 14, 161 (1971).

OLD, L.J., BENACERRAF, B., CLARKE, D.A., CARSWELL, E.A., STOCKERT, E.: Cancer Res. 21, 1281 (1961).

SIMMLER, M.C., SCHWARZENBERG, L., MATHÉ, G.: Cancer Immunol. Immunoth. in press (1976).

SKIPPER, H.E., SCHABEL, F.M., WILCOX, W.S.: Cancer Chemoth. Rep. 35, 1 (1964).

SKIPPER, H.E., SCHABEL, F.M., WILCOX, W.S.: Cancer Chemoth. Rep. 45, 5 (1965).

SKIPPER, H.E., SCHABEL, F.M., WILCOX, W.S.: Cancer Chemoth. Rep. 51, 125 (1967).
SNELL, G.D.: p. 338, in "The Physiopathology of Cancer" (F. Homburger & W.H. Fistman, eds.). 1 vol. New York: Hoeber-Harper 1953.
THOMPSON, R.B., MATHÉ, G.: Transplant. Rev. 9, 54 (1972).

Chapter 2
Biological Basis: Tumour Associated Antigens, the Immune Machinery, and Its Behaviour Concerning Cancer Cells

Only a brief summary will be given of the present concepts concerning these subjects.

2.1. Tumour Associated Antigens

A monograph (KOLDOVSKI, 1969) in the series to which this book belongs, has been devoted to the problem of tumour-associated antigens (TAA).

FOLEY (1953) opened the field with an in vivo method: he induced a sarcoma in mice with methylcholanthrene (MCA), and showed that, after the tumour had been removed, sufficient immunity had developed to inhibit reimplantation.

This fundamental discovery was confirmed by several groups, mainly by PREHN and MAIN (1957) and by KLEIN *et al.* (1960). The workers immunized a group of mice with an isogeneic MCA induced tumour, and another group with normal tissue, from the donor of the neoplasia: animals preimmunized with the tumour were resistant to challenge with their neoplasia, while those preimmunized with normal tissue presented a similar growth of the tumour as in the controls. The second group of researchers showed that, by immunizing syngeneic mice with UV-treated tumour cells from a primary MCA-induced sarcoma, they could be immunized against the corresponding line of neoplasia, but not against any other of the 12 lines of MCA sarcomas obtained in the same strain of mice.

Much complementary work has been devoted to *chemically induced tumour*-associated antigens. Many more carcinogens have been shown to induce TAA: benzopyrene (OLD *et al.*, 1962), dimethylbenzanthracene (PREHN, 1960; KOLDOVSKI, 1961), azodyes etc. (KLEIN, 1966; LAW, 1970).

Soon after, *virus induced tumours* were shown to also contain TAA (SJÖGREN *et al.*, 1961). In adult mice infection with polyoma virus produced resistance to transplant of a tumour induced by the same virus. Mice immunized with a small number of polyoma cells were also resistant to further graft of a great number of tumour cells. Neoplasias induced by *DNA viruses* (polyoma, SV-40, Shope papillomas etc.) or *RNA*

viruses (RAUSCHER, MOLONEY etc.) have been the object of extensive studies which have all shown that they contain TAA (KLEIN, 1966; LAW, 1970).

However, while chemically induced tumour-associated antigens vary from one tumour to another, even when the tumours are induced by the same carcinogen in the same strain or in the same animal, TAA of neoplasias induced by a virus are the same in all tumours induced in different animals of the same strain, or of different strains and even of different species (KLEIN, 1966; LAW, 1970).

Although the histocompatible graft reaction use of tumour graft in isogeneic animals is the best method to demonstrate the presence of antigens concerned in immunotherapy, because it reveals those antigens which are responsible for the possible rejection of an autologous tumour, other methods have been applied on experimental and on human neoplasias. These *methods* have shown that there is not one TAA, but several, which can be distinguished according to their situation (a) on the cell surface (those which are involved in cancer rejection, hence in immunotherapy), (b) in the cytoplasm, or (c) in the nucleus (Fig. 2.1).

These methods may be based on antigen-antibody reactions (the antibody being autologous and spontaneous or produced by allogeneic or heterospecific immunization and must, in the latter case, be purified by absorption with normal tissues of the same strain of animal as that of tumour cells). Other techniques such as immunodiffusion, cytotoxicity, complement fixation etc. can be used (LEVY *et al.*, 1972; WINN, 1972) (see appendix).

In addition to the serological demonstration of TAA, there are methods that depend upon cell-mediated immune responses. The techniques commonly used are in vitro techniques: the lymphocyte blastogenic response to TAA in either cellular or soluble form, the evaluation of the cytotoxic activity of lymphocytes towards tumour cells,

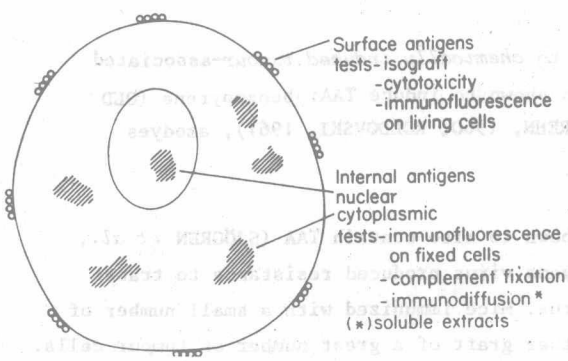

Fig. 2.1. Scheme of tumour associated antigens