Contents

Preface \hfill v

1. Introducing Cancer \hfill 1

2. Boveri’s Theory of Cancer was Ahead of its Time \hfill 12
   2.1 Aneuploidy theory “Got Lost” \hfill 17

3. Genesis of “The Enemy Within”? \hfill 22
   3.1 Clonal cancer \hfill 29
   3.2 Tumorigenic retroviruses \hfill 34
   3.3 Dominate oncogenes \hfill 42
   3.4 Tumor suppressor genes \hfill 46
   3.5 Driver genes \hfill 50

4. Gene Mutation Theory of Cancer \hfill 54
   4.1 “Carcinogens are mutagens” \hfill 56
   4.2 Retroviral oncogenes \hfill 57
   4.3 Are “cellular oncogenes” like retroviral oncogenes? \hfill 59
   4.4 Updated gene mutation theory is popular but unconfirmed \hfill 63
      4.4.1 Gene mutation theory cannot explain non-mutagenic carcinogens and tumor promoters \hfill 64
      4.4.2 No cancer-specific gene mutations \hfill 65
      4.4.3 “Causative” mutations are not clonal and not shared by all cells of a tumor \hfill 65
      4.4.4 Mutant genes do not transform normal cells into cancer cells \hfill 66
      4.4.5 Mutagenic carcinogens should cause instant transformation \hfill 68
      4.4.6 Gene mutation should have reproducible consequences \hfill 70
4.4.7 Non-selective phenotypes are not compatible with gene mutation 71
4.4.8 Cancer causing genes are hard to reconcile with human survival 72
4.4.9 Mutator phenotype to the rescue 73
4.4.10 Gene mutation does not explain chromosome instability in cancer 76
4.4.11 Karyotypic–phenotypic cancer cell variation is orders of magnitude higher than gene mutation rates 77
4.4.12 Cancer phenotypes are too complex for conventional mutations 78
4.4.13 Ubiquity of aneuploidy in cancer is not explained by the mutation theory 79

5. The Chromosomal Imbalance Theory of Cancer 85
5.1 Heuristic explanation of how chromosomal imbalance (and not gene mutation) generates cancer phenotypes 87
5.2 Aneuploidy causes chromosomal instability—the hallmark of cancer 89
5.3 Cancer is a progressive somatic aneuploidy syndrome 95
5.3.1 Exact correlations between aneuploidy and cancer 97
5.3.2 Origin of aneuploidy 98
5.3.3 Carcinogens induce aneuploidy 99
5.3.4 Carcinogenesis from aneuploidy is much more probable than via mutation 100
5.3.5 Multi-drug resistance and other complex phenotypes are more probable from aneuploidy than mutation 101
5.3.6 Preneoplastic aneuploidy 102
5.3.7 Cancer-“specific” (non-random) aneusomies 106
5.3.8 Clonal aneuploid karyotypes: stability within instability 108
5.3.9 Chromosomal instability is proportional to the degree of aneuploidy 112
5.3.10 Chromosomal instability drives cancer progression without gene mutation 113
5.3.11 Autocatalyzed progression of aneuploidy 115
5.4 Quantitative analysis of how aneuploidy generates new cellular phenotypes 118
5.4.1 The effect of aneuploidy on genomic stability can be quantified 128

6. Theory of Chromosomal Imbalance Solves Mysteries and Paradoxes 132
6.1 Carcinogenesis is dependent on aneuploidy and not mutation 132
6.1.1 Mutations of cancer cells as a consequence of aneuploidy 135
6.1.2 Cancer is not heritable because aneuploidy is not 136
6.1.3 Long neoplastic latencies are due to slow progression of aneuploidy 138
6.1.4 High rates of karyotypic–phenotypic variations and “immortality” 144
6.1.5 Karyotypic evolution of cancer 145
6.1.6 The phenotypes of genomically unstable cells are usually dominant 148
6.1.7 Cancer-“specific” chromosomal alterations 149
6.1.8 Cancer is a progressive somatic aneuploidy syndrome with complex phenotypes 150
6.1.9 Non-selective phenotypes such as multi-drug resistance 151
6.1.10 Paradox of karyotypic stability–within–instability of cancers 151

6.2 Autocatalyzed progression of aneuploidy is carcinogenesis 154
6.2.1 The Hayflick limit is due to the autocatalyzed growth of aneuploidy 155
6.2.2 The sigmoidal age distribution of human cancer 164
XVIII   Contents

6.2.3  Tumor formation 168
6.2.4  Drug resistance is an inevitable consequence of aneuploidy 174
6.3  Aneuploidy causes the Warburg effect by increasing ATP demand 176
6.4  Balanced mitotic forces and species-specific sequential chromatid separation may govern the rate of transformation 180
6.5  Cancer vaccine is very unlikely 186
6.6  “Cancers are a genuine type of species” 188

7.  New Perspectives for Cancer Prevention, Diagnosis and Therapy 195

7.1  International regulation of aneuploidy-inducing agents 199
7.2  Cancer detection 202
   7.2.1  Quantification of aneuploidy for diagnosis and prognosis 204
   7.2.2  Chromosomal imbalance theory applied to transcript microarray data 212
7.3  Cancer therapy 220
   7.3.1  Spontaneous tumor disappearance 224
   7.3.2  Induction of fever as cancer treatment 226

8.  Conclusion 235

References 240
Index 317
Color Plate Section 325
Preface

*Tumors destroy man in an unique and appalling way, as flesh of his own flesh, which has somehow been rendered proliferative, rampant, predatory, and ungovernable. They are the most concrete and formidable of human maladies, yet despite more than 70 years of experimental study they remain the least understood.*

(Rous 1967)

The broadly held conviction among researchers is that cancer ultimately results from an abnormality of the genome. The two principal competing theories on the nature of that abnormality is the subject of this book: Molecular medicine's search for the “material” cause of cancer in the form of gene mutations, and the chromosomal imbalance explanation that cancer results from global alterations in the dynamical relationships among all the genetic and metabolic activities of a cell independent of gene mutations.

In 1969, President Nixon proposed to reduce the budget of the National Cancer Institute (NCI). However, faced with the magnitude of the cancer problem, plus other political considerations, Nixon reversed himself embracing as his own the National Cancer Act sponsored by Senators Kennedy and Rogers and declared a national “war on cancer” in 1971 (Rettig 2006). Planners of this war predicted that technology would conquer cancer as it had conquered space and molecular biology would lead the way.

In 1986, John Bailar and Elaine Smith of the Harvard School of Public Health assessed the overall progress against cancer during the years 1950–1982. In the United States, these years were associated with increases in the number of deaths from cancer, in the crude cancer-related mortality rate, in the age-adjusted mortality
rate, and in both the crude and the age-adjusted incidence rates, whereas reported survival rates (crude and relative) for cancer patients also increased (Bailar and Smith 1986). Notwithstanding progress on minor fronts, they concluded we are losing the war against cancer.

Eleven years later, Bailar and Gornik took another look at how the campaign was going and declared the war against cancer is far from over (Bailar and Gornik 1997). “Will we at some future time do better in the war against cancer?” the authors asked. “The present optimism about new therapeutic approaches rooted in molecular medicine may turn out to be justified, but the arguments are similar in tone and rhetoric to those of decades past about chemotherapy, tumor virology, immunology, and other approaches. In our view, prudence requires a skeptical view of the tacit assumption that marvelous new treatments for cancer are just waiting to be discovered.”

In 2004, three federal reports (The CDC’s Morbidity and Mortality Report, June 25, The Annual Report to the Nation on the Status of Cancer, published in Cancer, July 1, and “Living Beyond Cancer: Finding a New Balance” issued by the President’s Cancer Panel in early June) said the number of cancer cases in the United States had reached a new high, and more people are alive after a diagnosis of cancer than ever before (Twombly 2004). It was not clear exactly what that declaration meant, however. Some took this to mean there had been marked progress in the treatment of cancer. Others were quick to question the implied widespread treatment success, saying the numbers are inflated by increased detection of non-lethal cancers by screening and there was no information on the quality of life. Even Julia Rowland, director of the NCI’s Office of Cancer Survivorship said, “The effect of including those cancers in the data pool is that 5-year survival rates increase because more people who may never have otherwise known they had cancer are now considered survivors, thereby masking the more important question of whether progress has been made in treating advanced solid tumors.”
John Bailar, professor emeritus of health studies at the University of Chicago agreed. He pointed out that the reports by the CDC and the President’s Cancer Panel directly compared “survival” between two different time frames decades apart. He said that made no sense given the potential for over-diagnosis by increased screening. Even more recently, a 2005 article (Leaf 2004) and two books (Epstein 2005, Faguet 2005) pulled few punches criticizing the paltry progress and dashed hopes in the war on cancer.

In an editorial titled “Our Contribution to the Public Fear of Cancer”, Bernard Strauss said, “the scientific community has managed to confuse the public about the causes of cancer and to add to an almost irrational fear of the disease. The only way to allay this fear is to development effective treatment and to understand how cancer develops… . The public’s responses to discussions of cancer are reminiscent of societies responses to the threat of epidemics before the nature of infectious disease was understood” (Strauss 1998).

What is the public to make of the confusion caused by the experts themselves? The public’s dread of cancer and the fear of plague in the Middle Ages have this in common: no rational explanation for the disease and no way to combat it. But what makes cancer so intractable and mysterious, the biological equivalent of Fermat’s last theorem? The answer lies in the way scientists and clinicians have been looking at the problem. Most cancer researchers think they already know the basic cause of cancer: genetic mutations in specific genes (Strauss 1998). However, the gene mutation hypothesis has not led to an understanding of even the most basic questions of how cancer starts and progresses. For example, in a commentary in the Proceedings of the National Academy of Sciences, Boland and Ricciardiello asked: “How many mutations does it take to make a tumor?” (Boland and Ricciardiello 1999). The answer was apparently 11,000 (Stoler et al. 1999). Boland and Ricciardiello rightly asked how does this result fit with central concepts such as clonal expansion and multi-step carcinogenesis? Indeed, questions that go to the heart of the mutation theory, which currently says only 4–6 mutations (Hahn and Weinberg 2002b) are needed to cause cancer.
If the current doctrine that cancer is caused by gene mutations was on the right track, the confusion and debate among cancer experts should have diminished in recent years instead of accelerating. Furthermore, cancer statistics should by now show obvious signs of progress but they don’t. The worsening situation is leading some cancer researchers to look for an escape from the quagmire of mutation theory. What is needed is a new, more productive way to think about cancer.

The solution one comes up with depends strongly on how one looks at the problem. To see this, consider your favorite puzzle or even better, a well executed magic trick. A world-class magician produces surprise and delight by negating everyday experience and shattering the rules of causality. The magic in the magic trick is to make the audience look at the trick in such a way as to make it appear incomprehensible, unfathomable, impenetrable, baffling, perplexing, mystifying, bewildering—how cancer appears today. However, looking at the same magic trick in a different way (the way another magician would) reveals it to be completely consistent with the logic of how things happen. Once the trick is revealed, the magic disappears and the rational world is restored. By looking at the cancer problem in a different way it is possible to lift the shroud concealing the unifying simplicity behind cancer.

Interest in cancer cytogenetics influenced human cytogenetics much more profoundly than is currently appreciated. For example, the main goal behind the study that eventually led to the description of the correct chromosome number in man was to identify what distinguished a cancer cell (Tjio and Levan 1956). The motivation was not primarily an interest in the normal chromosome constitution, which at that time had no obvious implications, but the hope that such knowledge would help answer the basic question of whether chromosome changes lay behind the transformation of a normal cell to cancer (Heim and Mitelman 2009).

Normal human cells turned out to have 23 different chromosomes that come in pairs, half from each parent, to yield a total of 46 chromosomes. Such cells are said to be “diploid.” Cells found in solid tumors, on the other hand, typically have 60–90
chromosomes (Shackney et al. 1995a). Their ploidy is “not good,” in other words, and the Greek term is “aneuploid.” It is a word you will have a hard time finding in the cancer chapters of the leading textbooks of biology.

Recall that the genes (of which there may be 25,000 or so in humans (Collins et al. 2004)) are strung along the chromosomes, so that each chromosome contains thousands of genes. Any cell with a chromosome number different from 46 and not an exact multiple of 23, or with an abnormal complement of chromosomes that add up to 46, is an aneuploid cell. Thus, aneuploid cells contain an imbalance in the complement of genes and chromosomes compared to the normal or “diploid” cell. This imbalance in the chromosomes leads to a wide variety of problems, one of which is cancer.

Another problem caused by aneuploidy that is familiar to most people is Down syndrome. This results when a baby is born with three copies of chromosome 21 instead of the normal two. Just one extra copy of the smallest chromosome, with its thousand or so normal genes, is sufficient to cause the syndrome (Shapiro 1983). Most Down fetuses are spontaneously aborted. Nonetheless, the imbalance is small enough (47 chromosomes) to permit occasional live births. The level of aneuploidy is therefore far below the threshold of 60–90 chromosomes found in invasive cancer, but it gives these patients a head start toward developing the same cancers that normal people get. Down syndrome patients have up to a 30-fold increased risk of leukemia, for example, compared to the general population (Patja et al. 2006, Shen et al. 1995, Zipursky et al. 1994).

There is one important difference between the small chromosome imbalance found in Down syndrome, and the more pronounced aneuploidy of cancer cells. With Down syndrome, the defect occurs in the germ line and so the chromosomal error is present in every cell in the body. But the defect that gives rise to the unbalanced complement of chromosomes in cancer cells is “somatic.” That is, it occurs in a particular cell after the body is formed. In the course of life, cells constantly divide by a process called mitosis. When errors in mitosis occur, as they often do, the possibility exists that a daughter cell will be aneuploid.
Aneuploidy destabilizes a dividing cell in much the same way that a dent disrupts the symmetry of a wheel, causing ever-greater distortions with each revolution. As aneuploid cells divide, their genomes become increasingly disorganized to the point where most of these cells stop dividing and many die. But rarely, and disastrously, an aneuploid cell with the right number and combination of chromosomes wins the genetic lottery and keeps right on going. Then it has become a cancer cell.

Cells with a normal number of chromosomes are intrinsically stable and not prone to transformation into cancer. What, therefore, causes normal cells to become aneuploid? That is a hotly contested question. It is known, however, that radioactive particles striking the nucleus or cytoplasm either kill or damage a cell. When the damaged cell then divides by mitosis, an error may arise leading to chromosomal imbalance. In short, radiation can cause aneuploidy. And certain chemicals, such as tars, also give rise to aneuploid cells. Tars and radiation sources are known carcinogens. In fact, all carcinogens that have been examined do cause aneuploidy.

That is a strong argument for the aneuploidy theory of cancer, but in order to understand the controversy one must understand the alternative theory. Everyone has heard of it because it is in the newspapers all the time. It is the gene mutation theory of cancer. According to this theory, certain genes, when they are mutated, turn a normal cell into a cancer cell. This theory has endured since the 1970s, and more than one Nobel Prize has been awarded to researchers who have made claims about it. One prize-winner was the former director of the National Institutes of Health, Harold Varmus. According to some researchers, the mutation of just one, or perhaps several genes, may be sufficient to transform a normal cell into a cancer cell.

In contrast, aneuploidy disrupts the normal balance and interactions of many thousands of genes, because just one chromosome typically contains thousands of genes. And a cancer cell may have several copies of a given chromosome. For this reason alone, aneuploidy is far more devastating to the life of a cell than a small handful of gene mutations.
The fundamental difference between the chromosomal imbalance theory and the reigning gene mutation theory may be put this way. If the whole genome is a biological dictionary, divided into volumes called chromosomes, then the life of a cell is a Shakespearean drama. If one were to misspell a word here and there, in *Hamlet* for example, such “mutations” would be irrelevant to the vast majority of readers, or theater-goers. A multicellular organism is at least as resistant to “gene mutations” as a Shakespeare play.

On the other hand, without “mutating” a single word, one could transform the script of *Hamlet* into a legal document, a love letter, a declaration of independence, or more likely gibberish, by simply shifting and shuffling, copying and deleting numerous individual words, sentences and whole paragraphs. That is the literary equivalent of what aneuploidy does. The most efficient means of rewriting a cell’s script is the wholesale shifting and shuffling of the genes, which aneuploidy or chromosomal imbalance accomplishes admirably.

Aneuploidy is known to be an efficient mechanism for altering the properties of cells, and it is also conceded that aneuploid cells are found in virtually all solid tumors. Bert Vogelstein of Johns Hopkins University has said that “at least 90 percent of human cancers are aneuploid.” The true figure is 100 percent since there is not one confirmed diploid cancer (Section 4.4.4).

Nonetheless, the presence of mutations in a handful of genes continues to be viewed as a significant, even a causal factor in carcinogenesis, even though any given mutated gene is found in only a minority of cancers. Cells with mutated genes can indeed be found in cancerous as well as normal cells, but it is becoming increasingly clear the vast majority of mutations are innocuous. Hence they are readily accommodated during the expansion of barely viable aneuploid cells as they compete for survival with their more viable chromosomally balanced counterparts. The current emphasis in cancer research on the search for mutant genes in a perpetual background of aneuploidy is a classic example of not seeing the forest for the trees.

Thomas Kuhn remarked that the great theoretical advances of Copernicus, Newton, Lavoisier, and Einstein had less to do with

What would gravely weaken the aneuploidy theory would be confirmed cases of diploid cancer (in which the tumor cells have balanced chromosomes), and with the culprit genes found lurking in every cell. That would go a long way toward proving the gene mutation theory. But where has that been demonstrated? It would be a front-page story. The truth is that researchers have not yet produced any convincing examples of diploid cancer.

In fact, the evidence is going the other way. There is a growing list of carcinogens that do not mutate genes at all (Section 4.1.4). In addition, there are no cancer-specific gene mutations (Section 4.4.2). Even tumors of a single organ rarely have uniform genetic alterations (Section 4.4.3). And, in a rebuttal that should be decisive, no genes have yet been isolated from cancers that can transform normal human or animal cells into cancer cells (Section 4.4.4). Moreover, the latent periods between the application of a carcinogen and the appearance of cancer are exceedingly long,
ranging from many months to decades, in contrast the effects of mutation are instantaneous (Section 4.4.5).

The goal of billions of dollars and decades of research was to come up with a clear and simple statement of how cancer genes cause or promote cancer. This was certainly the hope and expectation of most cancer researchers. One of the hallmarks of a bad theory is when its evolution becomes so complex and confused that experts in the field have difficulty explaining it. Thomas Ried, a major researcher at the National Cancer Institute in Bethesda, recently labored to...

speculate that the activation of specific oncogenes, and the inactivation of tumor suppressor genes act in concert with the deregulation of genes as a consequence of low-level copy number changes that provide the metabolic infrastructure for increased proliferation. One of the challenges in understanding the genome mutations in carcinomas will be to elucidate whether the presence of a tumor suppressor gene on frequently lost chromosomes, or the presence of an oncogene on frequently gained chromosomes is sufficient to fully explain the reason for the defining and recurrent patterns of genomic imbalances. In other words, we will need means to experimentally dissect the relative contribution of specific oncogene activation vis-a-vis the global transcriptional deregulation imposed by chromosome-wide copy number changes. Only then will we be in a position to truly verify or falsify Boveri’s central statement, i.e., the dominant role of inhibiting and promoting chromosomes that formed the basis for his chromosome theory of cancer.

(Ried 2009)

The conceptual barriers to accepting aneuploidy as the cause of cancer are not trivial but they shrink in comparison with the political and sociological obstacles. US taxpayers have forked over hundreds of billions of dollars in the war on cancer only to find that after 40 years of battling viruses, “oncogenes”, and “tumor suppressor” genes we are losing the war (Epstein 1998). But it is a one-front war with almost no resources devoted to alternative approaches. In spite of a century of evidence implicating aneuploidy as the cause of cancer, a leading researcher guesses that, “If you were to poll researchers … 95 percent would say that the accumulation of mutations [to key genes] causes cancer” (Gibbs 2001).
The biotech industry has bet heavily on cancer diagnostics and therapeutics based entirely on the gene mutation theory. The highly publicized sequencing of the human genome, the commercialization of diagnostic tests for cancer genes (Arnold 2001, Hanna et al. 2001, Wagner et al. 2000), and the hype about Gleevec being “at the forefront of a new wave of cancer treatments [that] differs from other existing chemotherapies because it affects a protein that directly causes cancer” (McCormick 2001) make it even more difficult for researchers to consider the possibility that mutant genes may not cause cancer after all.

Max Planck said that, “A new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die, and a new generation grows up that is familiar with it” (Planck 1949). It is encouraging to see that a new generation of cancer researchers are more inclined to accept aneuploidy as an alternative to gene mutation.

Chromosomal imbalance theory shows how gene mutations are not powerful enough to cause cancer (Section 5.4). It explains how cancer is initiated (Chapter 5) and why progression takes years to decades (Section 6.1.3). It explains the global or macroscopic characteristics that readily identify cancer: anaplasia, autonomous growth, metastasis, abnormal cell morphology, DNA indices ranging from 0.5 to over 2, genetic instability, and the high levels of membrane-bound and secreted proteins responsible for invasiveness and loss of contact inhibition (Chapters 5 & 6). It explains the common failure of chemotherapy (Section 7.3) and why cancer cells often become drug resistant even to drugs they were never exposed (Sections 5.3.5 & 6.2.4). It provides objective, quantitative measures for the detection of cancer and monitoring its progression (Section 7.2). It suggests non-toxic strategies of cancer therapy and prevention (Section 7.3). The chromosomal imbalance theory is the most comprehensive, productive, and satisfying explanation of carcinogenesis. In short: The Autocatalyzed Progression of Aneuploidy is Carcinogenesis.

David Rasnick
Index

1000-fold age bias of cancer 133
1000-fold transcriptional activation 61
3 times larger than obviously normal nuclei 206
3T3 cells 40, 43-45, 62
Abnormal cell morphology 6
Abnormal chromosomes combinations 16, 106, 114
Abnormal gene expression 133, 239
Abnormal metabolism 15, 79, 107, 133, 153, 234
Abnormal metabolism of cancer cells 234
Activating mutations 53, 72, 88, 127
Adaptable plasticity 145
Age bias of cancer 133, 142
Agricola 3
Albert Levan 17, 106, 173
Alexander 30-34
Alfred Böcking 211
Alfred Knudson 27
ALL 81, 82, 232, 233
Ames 24, 55, 57, 200
Ames Salmonella Assay 200
An in vivo to an in vitro environment 198
Anaplasia 6, 189
Anatomical biochemistry 196
Aneugenic chemicals 200
Aneugenic potential 200
Aneugens 100, 105, 117, 200
Aneuploid cells 9, 16, 81, 85, 86, 96, 97, 115-117, 119, 123, 124, 129, 131, 135, 139, 141, 144, 145, 154, 156-158, 162, 168-173, 175, 185, 186, 188, 189, 214-216, 224, 230, 234, 238, 239
Aneuploid chromosomes are present at all stages of carcinogenesis 207
Aneuploid fraction φ 124, 126, 156-159, 161, 162, 167, 169-173
Aneuploidy and progression of cervical cancer 211
Aneuploidy-cancer dilemma 18
Aneuploidy impairs normal growth and development 94
Aneuploidy in the diagnosis and prognosis of all types of cancer 211
Aneuploidy in utero 103
Aneuploidy-inducing agents 199, 200
Aneuploidy initiates carcinogenesis 104
Aneuploidy is inevitably dominant 88
Aneuploidy is necessary and—if progresses—sufficient for carcinogenesis 238
Aneuploidy itself catalyses chromosomal instability 91
Aneuploidy syndromes 102, 105, 138, 150, 152
Aneuploidy theory 11, 16, 17, 87, 137, 149
Aneuploidy-tolerating mutations 94
Aneusomies 16, 18, 77, 83, 106-108, 134, 150, 206, 207
Anticancer agents 223
Anticancer vaccines 187
Anti-oncogene 44, 47-49
Apc 67, 74
Armitage and Doll 164-167
Array-based genomic hybridization 107
Asbestos fibers 99
Asymmetric mitoses 12
Ataxia telangiectasia 105, 137
Chromosomally unbalanced 9, 216, 229
Chromosome aberrations 15, 138, 144, 145, 151, 200, 202, 206
Chromosome instability syndromes 98, 104, 105, 154
Chromosome territories 182, 185
CIN 49, 89, 90, 115, 209, 220
Clonal cancer 29, 238
Clonal chromosome aberrations 145
Clonal evolution models 112
Clonal Karyotypes 58, 109, 134, 138, 205
Clonal origin of cancer 15, 133
Clonality of tumor 24, 30, 32, 110, 139
CML 59-63, 232, 233
Coley 226-229
Coley’s toxins 228-230
Complex phenotypes 79, 101, 119, 133, 136, 150, 153
Complexity theory 168
Concept of functional oncogene 40
Conceptual divide 87
Congenital aneuploidies 88, 104, 105, 137, 139
Control of gene expression 121
Control parameter, r 161, 164, 169, 170
Correlation between degree of aneuploidy and progression of cervical cancer 211
COSMIC 50
Critical part played by fever is oft en overlooked 230
Croton oil 8, 65
Crum 202, 206, 207
Cytogenetics 18, 25, 27, 80, 86, 90, 205
Cytokinesis 98, 184
Cytokinesis failure 98
D
D and γ 217, 219, 220
Data mining 213, 217
DATE analysis 216, 217, 219
David Hansmann 11, 12, 204
Demand for ATP production 176
Determining the presence or absence of neoplasia at all the grade levels 209, 211
Diagnoses based on gene mutation 203
Diagnosis and prognosis of all types of cancer 211
Diagnosis of cancer 202
Difference between a cancer genome and its germ line sequence 78
Diploid cancers 16, 80

Diploid hyperplasias 57, 67, 100
Distribution entropy D 219
DNA index attractor values 170
DNA indices 6, 117, 131, 134, 141, 170-173, 176, 209, 217, 219
DNA indices near 1.7 171, 172
DNA quantitative techniques 205
Dominant oncogenes 42
Down syndrome 88, 105, 108, 120, 125, 126, 158, 159
Driver genes 50, 51, 53
Driver mutations 51-53
Drosophila 54, 55, 88, 119
Drug resistance 6, 71, 77, 78, 92, 93, 101, 102, 107, 134, 141, 148, 151-153, 174, 175, 204, 222, 239
Dysplasias 57-59, 205
E
Ebers Papyrus 1
Ed Scolnick 40
Edwin Smith Papyrus 1
Effect of fever on cancer pain 229
Egyptians 1
Elser and Hamilton 213
Enemy within 222, 224
Entropy and disorder 173
Enzyme activity 121
Epigenetic 73, 89, 91, 92
Erling Norrby 23
European Medicines Evaluation Agency 223
Evolution in vitro 160
Evolution of the karyotype 198
Experimental carcinogenesis 64, 69
Explanatory Power of Competing Theories of Cancer 133
Exponential growth 7, 10, 11
Expression artifact 45
F
Facial cancer of the Tasmanian devil 110
Famous monograph of 1914 14
Fanconi anaemia 137
Feline sarcoma virus 35
Fever 223, 225, 226, 229-232, 234
Fever inducing infection 225
Flexible or dynamic equilibrium 93
Flux across membranes 177
Flux balance analysis 179
Flux control coefficient 156
Four medical advances have systemically eroded Coley's fever-inducing therapy for cancer 231
Friend 35, 46, 47
Functional biochemistry 196
Functional proof 5, 9, 62, 74, 75, 149
Functional test 52, 53
G
Galen 3
Gatekeeper 49, 236
Gene dosage effect 82, 89
Gene expression datasets 212
Gene knockout experiments 212
Generalized reconstructed karyotype 198
Genetic instability 6, 24, 28, 113, 115, 129, 131, 156, 219
Genetic programs 87
Genetic roadmaps 212
Genetic signatures 213, 217, 219
Genomic instability 49, 73-76, 89, 90, 101, 104, 144, 146, 220
Genomic plasticity 101
George Todaro 26
Gerald Dermer 39, 54
Greeks 1
Growth control parameter 169-171
H
Hahn 72, 74
Hanahan and Weinberg 28, 62, 65, 72, 118, 192
Hansemann 11, 12, 97, 174, 189, 204
Harold E. Varmus 23
Harris 12, 14-17, 19, 55, 61, 63, 66, 67, 70, 74, 77-79, 94, 102, 103, 113, 114, 120, 149, 153, 189, 190
Harting and Hesse 3
Hauschka 58, 70, 77, 79, 81, 94, 107, 112, 144, 145, 148, 190, 239
Hayflick 72, 144, 156, 160, 181
Hayflick limit 72, 156
HeLa cell line 108
Heng 109, 145-147, 155
Herceptin 222, 223
Hippocrates 2
Holliday 77, 78, 142, 143, 161
Hoption Cann 225-227, 229-231
Horrobin 118, 119, 136, 196, 199, 213
Horstmann 233
Huettel 91, 92, 213-216
Huxley 190, 194
Hypothetical cancer genes 48, 66, 67, 128
I
Hypothesis of cancer genes 48, 66, 67, 128
Immortal cell lines 39, 152, 181, 196, 197
Immortalized cells 40
Inappropriate normalization 215
Incidence-rate of cancer 166
Invasion and progression 154
Infection-induced tumor regression 229
Incidence-rate of cancer 166
Induction and progression 154
Infection-induced tumor regression 229
Infectious cancer 109
Initiation 4, 8, 18, 25, 31, 41, 54, 64, 66, 70, 74, 76, 85, 90, 91, 93, 97, 100, 101, 104, 117, 136, 139, 140
Interaction between tumor and patient 198
Invasive ductal carcinomas of the breast 219, 220
Invasiveness 6, 70, 71, 107, 134, 141, 153, 177, 239
Ionizing radiation 4
IPCS Harmonized Scheme for Mutagenicity Testing 201
Issue of congruence of in vitro and in vivo studies 199
J
J. Michael Bishop 23, 68
Johannes Fibiger 5
John Cairns 8, 43
John Hill 3
Index

Jonas salk 187
Judith Berman 95

K
Kacser and Burns 88, 120, 121, 127, 216
Karyotype 16, 19, 76, 81, 82, 87-90, 93, 94, 102, 106, 109, 111, 114, 119, 144, 148, 153, 154, 162, 173, 190, 191, 194, 198, 205, 206, 236, 238
Karyotype evolution 198
Karyotypes of permanent cell lines 197
Karyotypic evolution 82, 145, 147
Karyotypic heterogeneity 30, 112, 146, 147, 197
Karyotypic heterogeneity of tumors in vivo 197
Karyotypic instability 30, 106, 145, 162, 164
Karyotypic progression 108
Karyotypic-phenotypic instability 86
Karyotypic-phenotypic variability 77
Karyotypic-phenotypic variations 136, 144
Kinetic-free zones 118
Kinetics of cell growth 10
Kirsten 35, 36
Knudson 27, 46, 47, 55, 113, 137, 191

L
Latency 57, 62, 76, 106
Lengauer 30, 73, 74, 76-78, 80, 89, 98, 113, 130, 131, 142, 149, 164, 168, 175
Leslie Foulds 11
Leukemia 9, 19, 35, 59-62, 80, 81, 103, 105, 137, 176, 183, 196, 197, 232, 233
Leukemia virus 35, 60
Levan 17, 30, 70, 76, 79, 102, 104, 106, 107, 113, 139, 142, 144, 145, 152, 153, 155, 158, 160, 168, 173, 175, 181, 191, 239
Li and Nicklas 181, 185
Lifestyle 8, 200
Lilinsky 57, 65, 66, 101
Limitations of in vitro experiments 199
Limiting DNA indices 173
Limiting values of ϕ 173
Lindsey 86, 88, 94, 115, 119, 224
Linear growth regime 10, 11
Loess 215
Log-log plots of cancer death-rates 164
Long neoplastic latencies 102, 138, 139
Loss of contact inhibition 6, 177
Loss of heterozygosity 48, 77, 90
Ludwik Gross 35
Luigi Capasso 7

M
Mamaeva 40, 110, 144, 197-199
Mammalian genome 72
Marker chromosomes 40, 82, 83, 94, 103, 109-111, 155, 186, 188, 198
Mathematical formulations 121
Maximum level of disorganization consistent with viability 234
McDonough 35
Membrane-bound proteins 177
Metabolic control analysis 120, 156, 216
Metabolic flux 179
Metabolic functions 15, 141
Metabolic phenotype 121, 122-126, 128, 176
Metaphase-anaphase junction 183
Metaphase rosette 182
Metastasis 6, 28, 32, 33, 70, 71, 79, 93, 107, 134, 141, 151, 153, 239
Microarray 204, 212-217, 219
Microarray data from 36 invasive ductal carcinomas of the breast 219
Microsatellites 90
MIN 90
Mitelman 17, 18, 20, 58, 72, 77, 82, 86, 89, 90, 97, 107, 108, 110, 112, 113, 151, 152, 197, 204, 206
Mitotic forces 180, 181, 184-186
Mixed bacterial toxins 228
Modal number 40, 80, 81, 109, 130
Molecular crowding 179
Moloney 35, 36
Monosomies 98, 115, 197
More harm than good 202, 204
Morgan 54, 55
Morphological transformation 39, 104
Mühlbock 35
Müller 55, 56, 69, 191
Multi-drug resistance 6, 71, 78, 101, 102, 134, 148, 151-153
Multipolar mitosis 14
Multipolar spindle 98
Mustard gas 69
Mutated ras 59
Mutation hypothesis 48, 54, 55, 64, 72, 73, 164, 174, 176
Mutation rate 51, 72, 75
Quantitative changes to the genome 119
Quantitative model 38, 42
Quantum jump in all chromosomes in all of the stages of cervical cancer 206

R
Radiation 4, 31, 65, 69, 76, 100, 105, 138, 144, 175, 223, 234
Random karyotypic variations 85
ras 27, 38, 40, 43-46, 59, 61, 65, 66, 236, 237
Rauscher 35
rb gene 46-48
RBI 27
Recapitulation of cancer in vitro 119
Reciprocal translocation 60, 61
Regulatory guidelines 200, 201
Regulatory requirements of the European Union 200
Relevance of in vitro research 199
Retinoblastoma gene 27, 67
Retinoblastoma(s) 27, 28, 46-48, 67, 105, 137, 233
Retroviral oncogenes 23, 26, 44, 46, 56, 57, 59, 62, 68
Retroviral promoters 45, 46
Retroviruses 27, 34-37, 39, 41, 42, 56, 57
Richard Strohman 235
Risk factor 7
RNA tumor viruses 57, 58
Robert Huebner 26
Robert Weinberg 43
Roentgen 4
Rosner's prophecy 196
Rous 1, 5, 11, 19, 23, 25, 26, 34-36, 44, 46, 56-58, 64, 65, 69, 70, 85, 86, 100, 101, 138, 146, 152, 190, 191, 200, 224, 225
Rous sarcoma virus 19, 25, 26, 34-36, 44, 46, 58
Rubin 34, 40, 45, 58, 103

S
Scolnick 40
Scrambling of chromosome territories 185
Screening 203
Sea urchin 13, 14
Secreted proteins 6, 177
Sector-Ploidy-Profi ling 110
Self-organizing system 168-170
Shen 89, 105
Sigmoidal age distribution of human cancer 164
Simian sarcoma virus 41
Single-cell organisms 152, 199
Single nucleotide polymorphisms 204
Six recommended changes in cancer research 195
SNPs 204
Somatic mutation 22, 36, 47, 50, 54, 56, 57, 64, 67, 101, 191
Species-specific sequence of centromere separation 185
Species-specific sequence of chromatid separation 184
Specific aneusomy 77
Spindle apparatus 14, 101, 184
Spiroptera carcinoma 5
Spontaneous mutation rates 72
Spontaneous remission 11, 196, 225, 226, 232
Spontaneous transformation 31, 40, 104, 160, 186, 197
Spontaneous tumor disappearance 134, 224
Sporadic aneuploidy 91
Spriggs 102, 103, 113, 117, 205
Stability index S 129
Stability within instability 108, 109, 111, 151
Stanley and Kirkland 103
State variables F, RNA or DNA index, and φ 217
Stem line 80, 113
Stemline karyotype 106
Steven Hajdu 1
Steven Martin 25
Stochastic karyotypic aberrations 146
Structural rearrangements 50, 76
Surveillance, Epidemiology and End Results (SEER) Program 206
Survival advantage of the hyperploid cells 86, 115
Survivors of atomic bombs 69
Susmo Ohno 18
Sutton 13
SV-40 93, 100, 104, 116, 154

T
Temin 36, 58, 59
Tetraploidization 117
The patient and the cancer are an environmental whole 195
Theodor Boveri 13
Theory for the analysis of phenotypes 120
Thermotherapy 234
Time course of carcinogenesis 69, 70, 164
Torres 94, 96, 100, 115, 139, 215, 230, 234
Transcript microarrays 213
Transduction 26, 37, 38, 42, 45
Index

Transfection 38, 39, 45, 46, 48, 197
Transformation 17, 18, 25, 29, 31-33, 36, 39, 40, 42, 43, 45, 49, 59, 68, 73, 94, 98, 100, 104, 106, 116, 120, 154, 156, 160, 162, 164, 180, 184, 186, 197, 216
Transforming genes 36, 38, 46
Transforming genes of retroviruses 36
Transgenic mice 62, 66, 67, 136
Transgenic oncogenes 57, 59
Transmissible leukemogenic agents 35
Transplantability 34, 79, 107
Treatment 1, 2, 23, 69, 104, 118, 146, 158, 193, 197, 199, 220, 223, 226, 229-231, 234, 236, 239
Tripolar spindle apparatus 14
Trisomies 91, 98, 115
Trisomy 21 88, 91, 108
Tumor-associated antigens 177
Tumor beehive 168, 173
Tumor progression 18, 53, 93, 112, 153
Tumor promoters 64, 65, 69
Tumor regression 229, 230, 234
Tumor suppressor genes 20, 22, 27, 28, 44, 46, 50, 53, 56, 62, 64-67, 72, 74, 75, 90, 105, 133, 135
Tumorigenic retroviruses 34
Tumorigenicity 48, 104, 149
Two-step model of carcinogenesis 117
Types of genomic instability 90
U
Unicellular eukaryotic organisms 192
Untested and unjustified assumptions 199
UroVysion 209, 211
US Department of Health and Human Services 203
V
Van Valen 144, 191
Varmus 23, 29, 44, 55, 59
Viable limit of disorder 173
Vincent 109, 110, 188, 192, 194
Viral carcinogenesis 5, 41
Viral oncogenes 38, 42, 56, 57-59
Viral oncologists 5
Viral theory 5
Vogelstein 22, 49, 52, 55, 65, 68, 69, 72, 77, 87, 128, 135, 138, 142, 166, 167
v-src 25, 26, 38
W
Walter Sutton 13
Warburg effect 176, 180, 234
Watson and Crick 19, 35, 235
Weaver and Cleveland 50, 94, 97, 106
Weinberg 20, 27-29, 43-48, 62, 63, 65, 71, 72, 74, 118, 135, 192
William Coley 227, 228
World Health Organization 201
X
X-rays 9, 15, 16, 31, 55, 56, 69
Y
Yamagiwa and Yoshikawa 190