Cancer

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Human metastatic melanoma in vitro

in which it appeared as Appendix F.

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Symbols used:

§	Data from a non-human model, generality uncertain
®	Reference thus tagged is a review article
[*number*]	Reference to the correspondingly labelled part of the table or figure last cited in the text

Cancer

While great advances have been made against many human diseases, cancer still challenges us, and remains a major contributor to human misery. The last 50 years have seen many improvements in treatment and survival, but we are still no better at preventing or curing cancer than in 1950.

cancer	noun [mass noun] a disease caused by an uncontrolled division of abnormal cells in a part of the body. [count noun] a malignant growth or tumour resulting from such a division of cells.
malignant	adjective (of a tumour) tending to invade normal tissue or to recur after removal; cancerous. Contrasted with benign.
tumour	noun a swelling of a part of the body, generally without inflammation, caused by an abnormal growth of tissue, whether benign or malignant.

The New Oxford Dictionary of English[203]

1 The scourge of cancer

It is a rare person indeed who has not had their life scarred by cancer in some way. It seems that every family has a member, and every person, a friend, who has been stricken by cancer, suffered and ultimately died. Those afflicted must face the shock of diagnosis, with its attendant confrontation with mortality, make difficult choices concerning treatment, endure sometimes protracted, painful, disfiguring, nauseating, and even dehumanising therapy with no certainty of cure, wait anxiously for destiny to deliver its verdict, and, ultimately, may have to accept that their only prospect is a relentless decline into death. Simultaneously, those who surround them must deal with the realities of assisting a friend to live, and possibly to die, desperately wishing things were otherwise but being powerless to alter them. Cancer is indeed a potent and multi-faceted contributor to human misery.

With the advent of improved sanitation and nutrition, the appreciation of antisepsis, and the development of drugs, antibiotics and vaccines, most of the diseases that have ravaged humanity over history can now be controlled. Smallpox has been declared extinct, and polio will soon join it. Bubonic plague, cholera, and typhus are no longer the threat they once were and exist not through a lack of understanding of their character or effective therapies, but due to poverty, politics, and the motivation for corporate profit. The impacts of influenza, diphtheria, and tuberculosis have been substantially reduced by immunisation. With mortality due to these causes declining, others such as heart disease, stroke, and diabetes take on greater importance. Here too, preventative, medicinal, and surgical procedures exist to limit their impact. Old foes may have temporary resurgence, as with antibiotic-resistant tuberculosis and new strains of influenza. New diseases may be recognised and rise to prominence or fall to new therapies: AIDS; Creutzfeldt-Jakob Disease; Alzheimer's Disease; Ebola. Throughout this, cancer remains. While advances have been made on some fronts, overall incidence and mortality rates are higher now than ever before {*See 'Incidence, survival, and mortality', below*}. The armamentarium of medical science has thus far failed to meet this challenge.

2 The nature of cancer

Defining characteristics

Dictionary definitions provide a starting point and are entirely satisfactory for casual use, but here we must delve a little deeper. Cancer is not a disease in the sense that, for example, tuberculosis is a disease. No single causative agent exists and there is no classical set of symptoms at presentation that immediately identifies it; indeed, it can be entirely without symptoms until very late in its progression. It does not affect any particular cell-type, tissue, organ, individual, or even species, nor is any of these spared. It does not always progress at the same rate or in the same manner, nor is the outcome always the same. Cancer, rather than being a single disease, is a family of diseases that share a small set of common attributes.

Chief among these is the existence of an aberration of tissue homeostasis leading to inappropriate net cellular proliferation. Normally, this homeostasis is maintained by a metabolically regulated balance between cell division and cell death. In cancer, one, or more likely both, of these processes is disturbed. The second defining attribute, seen particularly in solid tumours, is the intrusion of these cells into adjoining tissue, termed local invasion. Together, these features form the minimum definition of cancer. A third characteristic is of relevance in animals that are more than ~1 cm in every dimension. Above this scale, it is unlikely that any tumour could grow to a troublesome size relying solely on diffusion for the supply of nutrients and the removal of waste. By presenting itself as a tissue under nutritive stress, a tumour can instigate the creation of new blood vessels to supply it, a process termed angiogenesis. These features together can cause sufficient deterioration in the function of both the tissue of origin and its environs as to be life-threatening. The final and most pernicious attribute of many cancers is their ability to cast cells into circulation that may lodge at distant sites and proliferate there, causing widespread secondary tumours. This process, metastasis, contributes most to the gravity of cancer as a disease, and greatly hinders effective therapy by requiring it to be systemic.

Incidence, survival, and mortality

Data from the National Cancer Institute of the USA for cancer incidence, survival and mortality[214] {Table 1} provide the sobering information that overall, both incidence and mortality rate have increased since 1950 [1]; we are no better now at preventing or curing cancer than we were then. While disturbing, this observation does not convey the dramatic improvements that have been made in five-year survival rates [2], or the greatly reduced mortality among those under 65 years of age, and in particular those under five {Table 2}. Together with this, but more difficult to quantify, have come dramatic improvements in the quality of life enjoyed following therapy, with vastly improved pain control and the availability of extensive rehabilitation.

SUMMARY OF CHANGES IN CANCER INCIDENCE AND MORTALITY, 1950-98 AND 5-YEAR RELATIVE SURVIVAL RATES, 1950-97

Males and Females, By Primary Cancer Site

Primary Site	All Races: Estimated Cancer Cases in 1998	All Races: Actual Cancer Deaths in 1998	Whites: Percent Change 1950-98: Incidence Total	Incidence EAPC	U.S. Mortality Total	U.S. Mortality EAPC	5-Year Relative Survival Rates (Percent) 1950-54	1989-97
Oral cavity and Pharynx	30,100	7,965	-40.0	-0.7	-39.0	-1.0	46	58.4
Esophagus	13,200	11,764	-2.7	0.3	24.6	0.4	4	15.1
Stomach	21,700	12,957	-78.9	-2.6	-81.6	-3.5	12	20.7
Colon and Rectum	135,400	56,973	0.6	-0.1	-38.2	-0.9	37	62.0
Colon	98,200	48,814	15.1	0.1	-24.9	-0.4	41	62.1
Rectum	37,200	8,159	-23.3	-0.7	-68.3	-2.8	40	61.5
Liver and Intrahep	16,200	12,381	180.1	1.9	34.9	0.5	1	6.1
Pancreas	29,200	28,335	13.7	0.0	16.1	0.1	1	4.2
Larynx	10,000	3,866	20.0	0.1	-18.5	-0.3	52	66.1
Lung and Bronchus	169,500	154,472	248.2	2.2	252.5	2.8	6	14.8
Males	90,700	91,397	169.1	1.3	185.5	2.3	5	13.3
Females	78,800	63,075	598.0	4.3	617.2	5.2	9	16.8
Melanomas of skin	51,400	7,431	477.3	4.1	160.4	2.1	49	89.0
Breast(females)	192,200	41,736	63.1	1.3	-14.7	-0.1	60	86.8
Cervix uteri	12,900	4,340	-78.6	-2.8	-76.7	-3.5	59	71.5
Corpus and Uterus, NOS	38,300	6,421	3.7	-0.5	-68.2	-2.2	72	85.8
Ovary	23,400	13,390	0.7	0.2	-4.8	-0.3	30	51.5
Prostate	198,100	32,203	194.2	3.2	-1.4	0.3	43	97.0
Testis	7,200	370	124.6	1.9	-72.5	-3.2	57	95.4
Urinary bladder	54,300	11,757	53.8	0.9	-35.0	-1.1	53	81.9
Kidney and Renal pelvis	30,800	11,484	130.6	1.9	36.4	0.6	34	62.1
Brain and Other nervous	17,200	12,666	69.4	1.1	43.9	0.7	21	31.0
Thyroid	19,500	1,182	155.3	1.8	-48.8	-1.8	80	95.4
Hodgkin's disease	7,400	1,311	13.9	0.2	-75.1	-3.5	30	84.0
Non-Hodgkin's lymphomas	56,200	23,434	185.1	2.8	138.1	1.6	33	54.2
Multiple myeloma	14,400	10,311	222.8	1.7	199.0	2.1	6	28.0
Leukemias	31,500	20,469	11.0	0.2	-6.1	-0.4	10	46.0
Childhood(0-14 yrs)	8,800	1,456	35.1	0.8	-68.4	-2.8	20	78.5
All sites excluding Lung and Bronchus	1,098,500	387,047	46.3	0.8	-20.8	-0.4	38	70.4
All Sites	1,268,000	541,519	59.3	1.0	3.1	0.2	35	63.1

EAPC = estimated annual percent change. Highlighting added.

Table 1: Cancer incidence and survival rates in the USA (1950–1997/8)[214]

All Primary Cancer Sites Combined

Age Group	1950	1975	1998	Estimated Annual Percent Change 1950-75	1975-98	Total Percent Change 1950-98
0-4	11.1	5.2	2.3	-2.8	-3.0	-77.5
5-14	6.6	4.7	2.6	-1.0	-2.8	-59.6
15-24	8.5	6.6	4.5	-0.7	-1.8	-48.2
25-34	19.8	14.6	10.9	-1.2	-1.1	-43.6
35-44	64.2	53.9	38.9	-0.4	-1.3	-38.4
45-54	175.2	179.2	134.2	0.2	-1.2	-22.6
55-64	394.0	423.2	385.9	0.3	-0.3	-0.7
65-74	700.0	769.8	830.2	0.4	0.4	19.4
75-84	1160.9	1156.0	1320.3	0.0	0.6	14.7
85+	1450.7	1437.9	1751.4	-0.2	0.9	21.5
All Ages	158.1	162.3	161.5	0.1	0.0	3.1

Mortality rates are per 100 000 of population. Highlighting added.

Table 2: Cancer mortality rates in the USA (1950–1998)[214]

3 The cause of cancer

Scope of aetiology

Our understanding of cancer aetiology has advanced from ascribing it to an excess of black bile, to failure of the lymphatic system, to flaws in the biochemical control of cellular proliferation, to defects in the interplay between the genome and its environment. The current scope of our enquiry ranges mostly from the molecular to the organismic, but excursions to scales beyond these are sometimes made.

The prerequisites for cancer

The defining characteristics of cancer introduced above impose restrictions on the context in which cancer can develop. The characteristic of cellular proliferation implies the need both for regulated cellular growth, lest cells swell or dwindle in size as they increase in number, and the near-perfect transmission of modus operandi from one cellular generation to the next, lest the ability to survive and propagate be lost. To say this may seem to be no more than to say that life is a prerequisite for cancer, a fundamental notion indeed, but there are further implications. The first is that the organism must be multicellular for there to be any distinction between cellular proliferation and organismic replication. The second is that the life span of the organism as a whole must be considerably greater than that of its constituent cells, or it would die before aberrant cellular proliferation could be of any consequence. This further implies that there must be continual death and replacement of cells within the organism. The characteristic of local invasion requires that the organism be comprised of functionally distinct cell-types organised into tissues. Functional diversity implies a controlled mechanism of cellular differentiation, which implies an external agency by which the fates of cells can be independently determined. The relationship between incubation temperature and hatchling sex in many reptile species is one example[§279]. The characteristic of angiogenesis implies that the proliferation rate of one cell-type can be influenced by another, as can tissue architecture. This leads to the formal requirement of a means of intercellular communication. Once this is granted, the possibilities for the control of cell differentiation are also expanded dramatically by allowing tissue patterning to be determined parentally, rather than physically, as exemplified by the role of morphogens in ontogenesis[®269]. The characteristic of metastasis requires the presence of a transport mechanism within the organism, further reinforcing the need for tissue differentiation.

Human tumorigenesis

Multi-step tumorigenesis

Ultimately, all life processes are the result of the interaction of the genome and its environment within the bounds of physical laws, and this is therefore true of tumorigenesis. Current theory holds that cancer begins with a single cell sustaining a transmissible alteration that confers on it some growth advantage over its neighbours. It may reduce dependency on extracellular growth stimulation, or reduce sensitivity to extracellular growth repression. It may be something that increases the probability that the cell will divide, or reduces the probability that it will die. The alteration may interfere with its ability to maintain its genome, thus increasing the chance that further growth-advantageous alterations may occur and propagate. This leads directly to the concept of multi-step tumorigenesis, where cells gradually accumulate new attributes and become increasingly abnormal. A corollary of this is that tumours are clonal, a much-overworked term. Here, 'clonal' cannot be construed to mean that all cells comprising a tumour at any stage are genetically identical, indeed, there may be great genetic variability within tumours. It must instead be taken to mean that tumours ultimately originate from a single progenitor cell, but since this is true of any tissue in the body, it is hardly a distinction. What makes this statement

of value is that tumours may be derived from a cell already substantially differentiated and so have attributes that are characteristic of a particular cell-type.

As stated, each alteration that confers a growth advantage must be transmissible. This is generally taken to be synonymous with heritable, that is, transmitted by a cell to its descendants during cell division, but it need not be so. Transmission by viral infection also figures in tumorigenesis, as with human papillomavirus (HPV)[®58] and Epstein-Barr virus (EBV)[®189]. Whatever the mode, the nature of the alteration cannot be so disruptive as to prevent its transmission. Thus a tumorigenic virus cannot kill its host cell before replicating, a somatic gene mutation cannot prevent cell division, and, at a higher level, carriage of a germ-line mutation cannot have a phenotype that is invariably lethal during childhood.

Tumour-suppressor genes and oncogenes

The attempt to understand the interaction between genome and environment benefits greatly from the overlaps among epidemiology, biochemistry, molecular biology, and molecular genetics. Thus environmental factors implicated in causing the critical alteration, carcinogens, have been identified; the natures of the alterations made have been characterised at a molecular level; and the implications of these changes at the cellular level have been explored. In this way, many carcinogens have been found to be mutagens, that is, agencies of genetic alteration, as with γ-radiation and benzo[*a*]pyrene. An extremely valuable tool has been the study of hereditary syndromes in which predisposition toward cancer is prominent among the symptoms[74]. This has led to the identification of many genes that play important roles in the development of cancer, oncogenes, or its prevention, tumour-suppressor genes {Table 3}. Often, when the protein products of these genes are characterised, they are found to interact functionally with others similarly implicated in tumorigenesis. This has led to the identification of protein groups whose elements cooperate to perform a complex, often multi-step function, and this ability may be lost or degraded with the failure of any element. The functions performed by these subsystems are exactly those that would be expected given the prerequisites for the development of cancer. They participate in the control of cellular proliferation and differentiation, genome integrity, and intercellular communication. Those elements that are critical to a subsystem, that link subsystems together, that participate in multiple subsystems, or that can subvert function, are in general those considered to be tumour-suppressors or oncoproteins.

The mutation versus aneuploidy debate

A correlation between gross chromosomal defect and cancer was recognised at least as early as 1914, in which year Theodor Boveri stated that cancer cells contained '*…einen bestimmten, unrichtig kombinierten Chromosomenbestand*' (translation: '…a certain set of incorrectly combined chromosomes') and that '*Dieser ist die Ursache für die Wucherungstendenz, die auf alle Abkömmlinge der Urzelle* […] *übergeht*' (translation: 'This is the origin of the tendency to rampant growth passed on to all descendants of the original cell'[25]. In addition to changes in chromosome structure, such as translocations, abnormal chromosome numbers (aneuploidy) are frequently seen, and a loss or imbalance of gene expression may result. It has been proposed that this may be a driving force behind tumorigenesis. With advances in molecular genetics allowing the characterisation of the genome down to the individual nucleotide, oncogenes and tumour-suppressor genes have been recognised, and mutations in these proposed as causes of cancer. That chromosomal aberrations and mutations both occur is not in dispute. The issue is: which is the cause and which the effect?

Familial adenomatous polyposis [149] **Colorectal cancer**, hepatoblastoma[85], thyroid cancer[33 119], brain tumours[99]		
APC[86 99]		Mediates adhesion dependence: with β-catenin[218 234], E-cadherin[117], GSK3β[302], WNT[205], and by regulating MYC[105] transcription. Involved in cell motility[22], microtubule polymerisation[185], and kinetochore function[76].
Turcot's syndrome[®122] **Colorectal cancer, brain tumours**		
APC[86 99]		see above
PMS2?[34 55]		**DNA base mismatch detection**[100 141]
HNPCC[®6 274]**; Muir-Torre syndrome** **Colorectal cancer, endometrial cancer,** stomach cancer[1]		
PMS2[188]	(4)	see above
PMS1[188]	(3)	**DNA base mismatch detection**[100 141]
MLH1[160]	(2)	**DNA base mismatch detection**[100 141] Component of the BRCA1-associated genome surveillance complex (BASC).
MSH2[152 249]	(1)	**DNA base mismatch detection**[100 141] Component of BASC. Forms a mismatch recognition complex with MSH6.
MSH6 [37 283]	(5)	**DNA base mismatch detection**[100 141] Component of BASC. Forms a mismatch recognition complex with MSH2.
TGFBR2?[163]	(6)	**Growth factor receptor serine/threonine protein kinase** Growth factor responsiveness[70]
Xeroderma pigmentosum[®143 ®150] **Trichothiodystrophy, neurological abnormalities, cutaneous carcinomas:** melanoma[137], squamous and basal cell carcinoma		
XPA[255]	(A)	**Damaged DNA binding protein**[285]
ERCC3[267]	(B)	**DNA helicase**[165]
XPC[156]	(C)	**Damaged DNA binding protein**[285]
ERCC2[75]	(D)	**DNA helicase**[248]
DDB2[187]	(E)	**Damaged DNA binding protein**[115]
ERCC4[236]	(F)	**DNA repair endonuclease:** with ERCC1[81]
ERCC5[193]	(G)	**DNA repair endonuclease**[95]
POLH[294]	(variant)	**DNA trans-lesion polymerase** = DNA pol-η[168]
ERCC6[47 167]	(CS)	**DNA-binding ATPase**[224]
Fanconi anaemia Birth defects, bone marrow failure, pancytopenia, cancer predisposition: acute myeloid leukaemia[290], oral squamous cell carcinoma[206], myelodysplastic syndrome, breast cancer[296]		
FANCA	(A)	Dual incision prior to inter-strand cross link repair, with ERCC4[148]
FANCB	(B)	Unknown
FANCC	(C)	Interferon-γ signalling via STAT1[200], G_2/M arrest via CDC2[145], CASP3 activation after ionising radiation[90], mediates Fas-sponsored apoptosis[139 273].
BRCA2	(D1)	Homologous recombination and DNA repair: with BRCA1 and RAD51[54]
FANCD2[260]	(D2)	Unknown
FANCE[57]	(E)	Unknown
FANCF	(F)	Unknown
FANCG	(G)	Unknown
Wiskott-Aldrich syndrome[®194] **Immunodeficiency, eczema, thrombocytopenia**, lymphoreticular tumours, leukaemias, lymphomas[50 144]		
WAS[97]		Signal transduction[7 91 198]: with EGFR[231], FYN[9]; BTK[91], modulated by CDC42 membrane GTPase[132 140]; independent of actin polymerisation[238] Cytoskeletal organisation[251]: chemotaxis[96], phagocytosis[154 162] Apoptosis[212] Megakaryocyte differentiation[179]
Ataxia telangiectasia[235 ®242] **Immunodeficiency**[292]**, lymphoma**[131 157 221], leukaemia[178 295], breast cancer[120 125 229]		
ATM[216 220]		**Serine/threonine protein kinase**[35] Known substrates[134]: BRCA1[49 82], nibrin[289 300], CHK2[169], p53[130], ABL[11], MDM2[56] DNA damage response[31 111 252]: as component of BASC; with CHK1[40], CHK2[169 261], MDM2[56], p53[130 183 280] DNA recombination: as component of BASC
Nijmegen breakage syndrome[63 235 ®265] **Immunodeficiency, lymphoma**		
NBN[264]		DNA damage response: as component of BASC[289 300]
Bloom's syndrome[®84] **Growth deficiency, telangiectasia, diabetes mellitus, cancer predisposition:** leukaemia, Hodgkin's lymphoma, oesophageal cancer		
BLM[67]		**DNA helicase**[126 158] DNA damage response: as component of BASC

Table 3: Hereditary conditions that predispose toward cancer (continues overleaf)

Hereditary retinoblastoma[®2 69] **Bilateral paediatric retinoblastoma,** osteosarcoma[166], melanoma[5 12 182], bladder cancer[181]	
RB1[62 108 161 225]	**pRB-related 'pocket protein'**[43] Cell-cycle progression (G_1)[101]: with E2F1 Control of differentiation[41]
von Hippel-Lindau syndrome[44 48 ®51 ®79 196] **Renal cell carcinoma, pheochromocytoma, CNS hemangioblastoma**, pancreatic cancer[164], astrocytoma[186], Hodgkin's disease[61]	
VHL[293 297]	**Transcription elongation inhibitor**[184] **Ubiquitin E3 ligase**[45] Growth factor response[202], via p27[133]
Wilms' tumour[®281]**; Denys-Drash syndrome**[159] **Paediatric kidney tumour**, leukaemia[208 250], breast cancer[237], adult renal cell carcinoma[30]	
WT1[94 177]	**Transcription factor**[65 153 276] Cell-cycle progression (G_1)[146], via RBBP7[88], p21[71] Apoptosis control via BCL2[172 177]
Multiple endocrine neoplasia[®257] **Endocrine tumours:** pituitary, parathyroid, pancreas**, peptic ulcer disease**, melanoma[191]	
MEN1[36]	**Transcription co-factor** Specifically binds and inhibits the JUND transcription factor[3]
Peutz-Jeghers syndrome[®175] **Adenocarcinoma**[23]**:** colon[64], breast, testis, ovary, biliary tract[247], pancreas[247], melanoma[92 217]	
STK11[107 123]	**Serine/threonine kinase**[240] Unknown function
Li-Fraumeni syndrome[®73] **Sarcoma, brain tumours**[24], breast cancer	
TP53[116]	**Transcription factor**[171] Apoptotic control[13 17 87]: via *BAX*[27], *BCL2*[180] Cell-cycle progression: via *CDKN1A*[66], *GADD45*[129] Genomic stability[26 271] DNA damage response[282]: with ATM[130 183 280] ATR[258], CHK1[233], CHK2[38 110 233 261]
CHEK2[16]	**Serine(/threonine?) protein kinase** DNA damage response: with ATM, p53[110 233 261] Cell-cycle progression: via CDC25[38]
Neurofibromatosis I[®192] **Fibromatous skin tumours, cafe au lait spots,** pheochromocytoma, meningioma, glioma, astrocytoma[142 151]	
NF1[287]	**GTPase-activating protein**[104] Signal transduction: modulates RAS activity[299]
Neurofibromatosis II[®72] **Bilateral acoustic schwannoma**, meningioma[263]	
NF2[136 173 201]	**Ezrin, radixin, moesin family (ERM) protein**[28 112 176] Cellular adhesion[93 138] and adhesion dependence[230]
Gorlin syndrome[®52] **Multiple developmental defects, basal cell carcinoma, medulloblastoma**	
PTCH[98 124]	**Trans-membrane receptor protein:** Sonic hedgehog signalling (with Smoothened)[245] Chromosomal stability[228]
Multiple hamartoma syndrome; Cowden syndrome[®68] **Multiple hamartomas (skin, mucous membrane, breast, thyroid, intestine)**, brain tumours, prostate cancer, melanoma[32]	
PTEN[239]	**Dual specificity (Tyr, Ser/Thr) protein phosphatase; lipid phosphatase** Cell-cycle progression (G_1): via PI3K[20 266], cyclin-D1[278], p21[288] and p27[155 278] Apoptotic control[277] Cell adhesion and migration[254]: via FAK[253]
Melanoma-astrocytoma syndrome[®128] **Melanoma, neural tumours, commonly astrocytoma**[8]	
CDKN2A[78]	**ARF: Degradation targeting**[210] Genome surveillance: with p53, MDM2[121]
Melanoma[103 272], leukaemia[4 195], mesothelioma[207 291], pancreatic carcinoma[29]	
CDKN2A[78]	**p16: CDK4/6 cyclin-dependent kinase inhibitor**[227] Cell-cycle progression (G_1): with pRB, cyclin-D, CDK4/6[232 268] Cellular senescence[114]
Melanoma[241]	
CDK4[303]	**Cyclin-dependent kinase**[102] Cell-cycle progression (G_1): with pRB, Cyclin-D, p16[232 268]

Table 3 (continued)

Gastric cancer[89]**, colorectal**[213] **cancer**, lobular breast cancer (?)[209 270]	
CDH1[18]	**Calcium-dependent cell adhesion protein (epithelial):** E-cadherin[19] Cell adhesion, tissue architecture, invasion suppression[21], metastasis[15] Contact inhibition and adhesion dependence: with APC[117], β-catenin, p27[243]
Proximal colorectal cancer[83 301], myelodysplastic syndrome[39]	
GSTT1[246]	**Glutathione S-transferase enzymes**[219] Chemical detoxification; free radical scavenging; tumour chemoresistance.
Ovarian cancer[14], lung cancer[223], colorectal cancer[301]	
GSTM1[204]	**Glutathione S-transferase enzymes**[219] Chemical detoxification; free radical scavenging; tumour chemoresistance.
Breast cancer, ovarian cancer[77]	
BRCA1[59 275]	DNA damage response: as component of BASC; with p53[199 298], ATR[259] Centrosome replication[113]
Breast cancer[286], pancreatic cancer[222]	
BRCA2[256]	Homologous recombination and DNA repair: with BRCA1 and RAD51[54]

Listed are hereditary diseases where: cancer predisposition is a facet of the symptomatology; an underlying gene has been identified; there is some understanding of the function of the encoded protein.

Ordering is to allow juxtaposition of apparently distinct phenotypic manifestations with the same underlying cause (for example, *APC* mutation), or similar phenotypic manifestations with differing underlying causes (for example, Li-Fraumeni syndrome). Beyond that, syndromes are grouped into broad similarity of tumour type (for example, melanoma predisposition).

Parenthesised items following gene names denote recognised sub-classifications of the disease.

Bold entries among the associated diseases denote those typical of the syndrome. Others are those also reported in hereditary disease, or implicated by virtue of gene aberrations found in sporadic cases. Bold entries among the functions of encoded proteins denote the functional class to which the protein product belongs, where this is well defined.

Table 3 (concluded): Hereditary conditions that predispose toward cancer

Proponents of aneuploidy as a cause[®226] cite the inherently low basal mutation rate, suggesting that alone, it could not account for the number of aberrations seen in many tumours given the time over which they develop. If, however, an early mutation has the consequence of increasing this rate, this argument fails. Consistent with this, mutations in genes associated with DNA repair mechanisms are frequently observed, as are mutations in genes associated with the maintenance of chromosomal stability. A reasonable interpretation of current information is that mutation and aneuploidy are inextricably linked, and once either occurs, the rates of both increase. A mutation may affect the maintenance of chromosomal stability and euploidy as easily as gain or loss of a chromosome may affect basal mutation rate. It is a self-reinforcing cycle that is as likely to be initiated by a chance event affecting one aspect as the other. The search to identify which is the cause, and which the effect, is both misguided and irrelevant.

The immune system and cancer

Many believe that the immune system has an important role in the prevention of cancer. That this is a fallacy becomes evident when it is appreciated that only in relatively few hereditary cancer predisposition syndromes is immunodeficiency present, and in the great majority of hereditary immunodeficiency syndromes, there is no associated predisposition toward cancer.

The progression of cancer

However the progression from normality to malignancy is driven, it appears to proceed through a number of reasonably well defined stages. In tissues of epithelial lineage, it will often begin with hyperplasia: the presence of supernumerary cells not significantly morphologically different from the normal tissue. Dysplasia develops, during which the morphology of the cells diverges from the norm for the tissue of origin. With increasing dysplasia, the growing benign tumour ultimately will warrant the

designation of carcinoma in situ. With invasion into surrounding tissue, the tumour becomes malignant, and if it spreads to distant sites, it has become metastatic.

While these changes may be occurring at the level of the tissue there may or may not be any outward indication of this process. Where symptoms are sufficiently obvious to prompt the seeking of medical advice, they often include lumps or swelling (the origin of the word 'tumour'), pain, fatigue, unusual bleeding or discharge, gastric, intestinal or urinary obstruction, fever, unusual sweating, deficient wound healing, or neurological effects including alteration in sensation or motor control. It is not unusual for cancer to be asymptomatic and discovered through intentional screening, or fortuitously as a result of other medical procedures such as blood tests, X-rays, ultrasound examination, or surgery. When symptomatic however, it is likely that the cancer has been present undetected for some years, and, in the case of solid internal tumours, it is likely that a blood supply to the tumour has already been established. Once cancer is suspected, various diagnostic tools will be applied to verify if this is indeed the case, and if so, to identify the particular type and its stage of progression. From there, a strategy for treatment can be developed.

The treatment of cancer

Conventional treatment

Three major modalities have been the mainstays of cancer treatment since its recognition as a cellular disease: surgery, chemotherapy, and radiotherapy. Clinical experience has led to the development of particular treatment regimens for particular cancer types at various stages, the principal determinant being the degree to which the disease has metastasised, if at all. Where medical imaging and biopsies of the tumour and adjacent lymph nodes indicate that spread in unlikely, a purely local treatment may suffice, typically surgical resection of the tumour and marginal normal tissue, or targeted radiotherapy, delivered either from an external source, or by isotopic implantation.

Where metastasis is known or suspected, a systemic treatment is required. This is generally in the form of chemotherapy using cytotoxic or anti-proliferative drugs. Variations, such as isolated limb perfusion, and combined modalities, such as surgery with local radiotherapy may also be employed. In all cases, whether it depends on the surgeon's skill, the precision of conformant radiotherapy, or the pharmacological and biological attributes of drugs, the efficacy of treatment depends on the discrimination between cancerous and normal cells and the selective extirpation of the former.

Immune system modulation

There is a school of thought that believes that the specificity of the immune system may be harnessed to provide the means of discrimination required. This process began long before the cellular basis of the immune system was known, with Coley's toxins in the nineteenth century. The late twentieth century saw the therapeutic use of recombinant cytokines, and today novel drugs that directly or indirectly affect immune system function are in clinical trial. Attempts have been made to create vaccines from mutated or over-expressed tumour antigens, with some success in animal models. Nevertheless, if no tumorigenic pathogen is present, these approaches may be limited.

The limitations of conventional therapies

To refer to conventional therapies as 'cutting, poisoning, and burning' illustrates well how blunt are the tools of surgery, chemotherapy, and radiotherapy. The greatest obstacles to the success of conventional systemic treatment are the dispersed nature of cancer as a disease and the extremely close biological similarity between malignant and normal cells. To date, the major objective of chemotherapy has been

the selective destruction of proliferating cells, the rationale being that cancer cells are more likely to be dividing. As we learn more about cancer, we are finding that this is perhaps a poor distinction at best. Firstly, the situation is not that every cell in a tumour is dividing more frequently than normal, it is that overall, there is a net excess of cell proliferation over cell death. Alterations to apoptotic mechanisms may be as important as increased cellular proliferative capacity. Secondly, very many normal tissues, such as gut epithelium and haematopoietic precursor cells have an intrinsically high proliferation rate and are therefore detrimentally affected by these drugs, often to the extent of being dose-limiting for therapy. Thirdly, tumour vasculature is both spatially and temporally heterogeneous, with consequences for the uniform delivery of drugs, and hence their efficacy. To overcome these obstacles, ways must be found to exploit the aspects of tumour biology that do differ from the biology of normal cells and tissues.

Novel therapeutic strategies

Gene and anti-sense therapies

In cases where tumour growth occurs only due to the functional failure of a tumour-suppressor, it may in future be possible to supply a replacement for a defective gene[®174], but there are immense problems in bringing such gene therapy to the clinic. In particular, delivery of the replacement gene specifically to tumour cells will be required where over-expression in normal cells is associated with toxicity. Even if delivery mechanisms can be developed, ensuring appropriate and sustained levels of gene expression are formidable obstacles.

Conversely, where tumour growth is supported by production of a mutant protein or over-production of a normal one, the possibility of specifically interfering with this exists. The most promising current approach to this is in the use of anti-sense agents[®53]. These are multi-base nucleic acid analogues whose sequence is the complement of the mRNA of the target protein. When delivered or expressed intracellularly, they will avidly bind such mRNA and interfere with its translation. This technique works well in vitro, but therapeutically, it faces many of the same problems as gene therapy.

Targeting signal transduction

It is now widely appreciated that many of the molecular causes of disease are either components of, or exert their influence via, intracellular signal transduction channels[®106], and this may be particularly true of cancer. If drugs that interfere with spurious proliferative signalling can be found or developed, a therapeutic opportunity may exist in the treatment of some types of cancer.

As a class, receptor tyrosine kinases make excellent potential therapeutic targets since their function is often altered in cancer by erroneous expression, mutation, or over-expression of their specific ligand[®304]. Where this has the effect of stimulating net cellular proliferation, it can drive tumorigenesis. As an example, several novel drugs have been developed that target the epidermal growth factor receptor and a number are now in clinical trial[109 211].

Non-receptor kinases, both tyrosine and serine/threonine, also frequently participate in signal transduction channels and have been implicated in many cancer types. Among theses are the cyclin-dependent kinases (CDKs) and other regulators of the cell division cycle, such as WEE1. Of particular interest is the recent FDA approval of imatinib mesylate for the treatment of chronic myelogenous leukaemia[46]. This drug is a tyrosine kinase inhibitor that counteracts the effects of the erroneous activation of the ABL kinase resulting from its expression as a BCR fusion protein after the chromosomal translocation characteristic of this cancer.

Another target is RAS, a signalling protein that is normally self-regulating. In many cancers however, this regulation is lost, and if triggered, RAS signalling remains active and can drive cellular proliferation. Its activation requires that it become associated with the cell membrane, and for this to occur, RAS must be post-translationally modified by farnesylation. Inhibitors of the farnesyltransferase enzyme that performs this may reduce or prevent aberrant RAS signalling. Compounds of this type are also in clinical trial[127].

Anti-angiogenic agents

In tissues produced by the normal processes of development and growth, the needs for nutrient and oxygen supply and waste removal are met by the co-establishment of a hierarchy of blood vessels and a network of lymphatic vessels. Since this is not the way in which tumours develop, this mechanism is not available to them. The manner in which cancers resolve this distinguishes them from almost all normal adult tissues: their continuing existence is dependent on their ability to induce angiogenesis. Therefore, therapies that target the proliferation, but not the survival, of vascular endothelial cells should prevent the growth of tumours and probably cause their regression, and do so with minimal toxicity[®42]. Two approaches to this exist, although in reality they may be different aspects of just one. Firstly, it should be possible to diminish or oppose the effect of growth factors that stimulate endothelial proliferation. This may entail the use of cytokine therapy, as has been used in the treatment of infant haemangioma with interferon-α, or of antagonistic antibodies directed against the receptors for critical growth factors, such as FGF2, VEGF, and angiogenin. Secondly, it may be possible to stimulate activity of the normal process that disables angiogenesis after wound healing and ovulation. Here, the anti-angiogenic properties of several small peptides that are cleavage products of proteins engaged in these processes may be extremely important. One such, angiostatin, a fragment of plasminogen, causes drastic regression of human breast, prostate, and colon tumours implanted into mice, and holds them in this state for the duration of treatment[§197]. While no anti-angiogenic drugs have yet been approved for the treatment of human cancer, at least fifteen are in clinical trial, and there is a very real prospect that some, at least, will be efficacious.

Anti-metastatic agents

Among the several hundred distinct normal human cell-types, only one, the leukocyte, has the ability to travel freely within and between tissues. Indeed, displacement of any other type of normal cell into an inappropriate context is generally sufficient to cause its immediate self-destruction though apoptosis, a process termed anoikis[80]. It is thought that this process is mediated through biochemical interactions between cells, and between a cell and the extracellular matrix. When the correct combination of signals is not available to a cell, that is, when it is displaced, it dies. In contrast, the most pernicious aspect of cancer, metastasis, implies that tumour cells can overcome these limitations. Clearly, there is more to metastasis than the fortuitous dislodgement of a cell or a clump of cells from a primary tumour, and some change in biological regulation must be taking place. To detach from the primary tumour, it must be able to decrease its intercellular affinity, and the proteins β-catenin and E-cadherin have been implicated in this role, particularly in gastric cancers[®190]. To be able to survive in isolation during its travels, it must attain at least substrate-independence, and the integrins are implicated here[®147]. In the case of individual cells, contact-independence must also be attained, and here again, E-cadherin or its signal transduction subsystem, has been implicated[284]. To move within and between tissues requires that it have inherent motility, implicating cytoskeletal components[§118 §173] and cytokine signalling, as with HGF/MET[®170]. It must be able to pass both between other cells that may normally be strongly cohesive,

and possibly through the basement membrane, and here, matrix metalloproteinases have been implicated[®244]. These processes must also work in reverse, in that the metastatic seed must be able either to adhere to, or exit through the vessel wall in order for a secondary tumour to form.

The possibility that these activities may be susceptible to modulation presents a therapeutic opportunity, and the search to elucidate the mechanisms governing metastasis, and for the means to influence it is now in progress. It is as yet too early to speculate on how successful this will be.

Pro-drugs

One approach to resolving the issue of general, as opposed to tumour-specific cytotoxicity has been to separate the delivery of a drug from its activation[®60]. In this way, a biologically benign pro-drug can be administered systemically and subsequently, its latent therapeutic function activated locally. This approach is open to a great many variations. Higher tumour pro-drug concentration may be achieved by taking advantage of poor tumour vasculature. Systemic pro-drug levels can be allowed to rise until a steady-state is reached, whereupon the majority of the pro-drug can be removed from well-vascularised normal tissue immediately prior to activation. Drug activation may be triggered by radiolytic cleavage, by tumour hypoxia or pH, or by enzymatic activity. In the latter case, endogenous enzymes expressed in the tumour tissue type, or over-expressed in the tumour may be used. Alternatively, exogenous enzymes may be employed. In antibody-directed enzyme pro-drug therapy (ADEPT), such an enzyme is supplied and is targeted to the tumour by a linked antibody. Upon pro-drug delivery, activation only occurs within the tumour. In gene-directed enzyme pro-drug therapy (GDEPT), a gene for the enzyme may be introduced into the tumour, albeit with difficulty, that is subject to tissue-specific expression. Finally, while much of the early work with pro-drugs has employed traditional cytotoxins such as mustard derivatives, there is a great range of potentially suitable agents.

Genetic targeting

A particularly cunning strategy to target tumour cells has been devised that harnesses two aspects of p53 molecular biology: its frequent functional loss in cancer cells, and its active disablement by many viruses as a prerequisite for productive infection. Onyx Pharmaceuticals have engineered an adenovirus, ONYX-015[®215], in which the gene responsible for disabling p53 upon infection is non-functional. In consequence, they believe, it will only be in cells where p53 is already non-functional that the virus can replicate, ultimately destroying the host cell in the process. Since all normal human tissues express functional p53, but it is mutated in most tumours, it will only be tumour cells that are destroyed. While attractive theoretically, our knowledge of p53 function is still incomplete, and opinion is divided on the soundness of the underlying premise and on what practical utility this approach will have. This issue will be clarified considerably with the completion of the clinical trials of ONYX-015 that are currently underway[135]. Also developed, but not yet to the same stage, is a similar virus that will target cells lacking the function of another tumour-suppressor, the retinoblastoma-associated protein, pRB.

4 Conclusion

The quest to find effective therapies for cancer is formidable indeed, but each advance we make in understanding the processes underlying it represents a possibility that a point of weakness will be found, and a new avenue for prevention or therapeutic intervention revealed. Our knowledge grows exponentially as increasingly delicate and incisive tools are applied to the tasks of investigating and influencing the workings of the cell. It is utterly inconceivable that this ongoing application of limitless human ingenuity and endeavour will not one day see the scourge of cancer defeated.

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