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THREE PERCENT (3%) EFFICACY OF CHEMOTHERAPY TREATMENT ON CANCER CURE

THE ORIGINAL CONCLUSION BASED ON FACTS 1985
SUBSEQUENT AND CURRENT VALIDATION OF THESE CONCLUSIONS 2004

BY CARLOS M. GARCÍA, M.D.

Many patients and support individuals not versed in *'Alternative'* medicine or as I see them, *insecure of options and responsibility of the consequences of* ***choice***, get incensed when I state that chemotherapy has a FAILURE RATE of ninety-seven percent (97%), or a cure rate of a mere three percent (3%). They are usually shocked and then appalled by this statement. Their body posture changes, their mood becomes more confrontational, in short this statement touches the very core of their belief structure. That is if I am correct, as I will attempt to corroborate with the attachments herein, then why were they not told this ***prior*** to being told that chemotherapy, along with surgery and radiation are the **ONLY** ways of treating cancer and furthermore that *alternative* practitioners are mere ***quacks.***

The **FACTS** are that after years of trying, and FAILURE and trillions of dollars in research with no improvement in success why is chemotherapy still being used? Are the oncologists just mindless heartless doctors in it for the buck? How do they justify **just** recommending chemotherapy, radiation and surgery, while ignoring dietary changers, and emotional issues? How do they **justify** the continued endorsement that was first known to be ineffective in 1985 and remains ineffective with a ninety-seven percent (97%) failure rate today?

In 1985 Scientific America Volume 253, Number 5, Pages 51-59 in the Article Entitled: *The Treatment of Diseases and The War Against Cancer,* by John Cairns: on page 59 the following is printed: ***"…*** ***All*** *told, adjuvant treatments now avert a few thousand (perhaps 2 or3 percent) of the 400,000 deaths from cancer that occur each year in the U.S. …"*

I grant you this was written in 1985. One could assume that between 1985 and say 2005, along with trillions of cancer research dollars, one would like to think that the cure rate has increased from a mere three percent (3%). Lets be honest, spontaneous remission, has a higher success rate than chemotherapy. So potentially one could reach the logical and perhaps factual conclusion that doing nothing when diagnosed with the symptom of cancer is a better medical choice than opting for chemotherapy, with definitely a higher quality of life than that presented by chemotherapy.

However, please realize that if everyone of you began to *think for themself* then the unemployment rate in America would most likely sky rocket since cancer is now the largest revenue generator in American Traditional medicine. In fact, I believe that the medical industrial complex is the second largest revenue generator for the American gross national product after its

military industrial complex. I suspect that the label "*war* on cancer" may have been influenced by our military prowess.

Twenty years later, more or less, several Australian ***oncologists*** and researchers, **Graeme Morgan**, from the Department of Radiation Oncology, Northern Sydney Cancer Centre, Royal North Shore Hospital, Sydney, NSW; **Robyn Wardy**, from Department of Medical Oncology, St Vincent's Hospital, Sydney, NSW; and **Michael Bartonz**, from Collaboration for Cancer Outcomes Research and Evaluation, Liverpool Health Service, Sydney, NSW, Australia undertook a meta-analysis, which is a fancy term for the combination of several related studies that address a set of related research hypotheses, in this case the efficacy of chemotherapy on the *five year survival* cancer patients entitled: *The Contribution of Cytotoxic Chemotherapy to 5-year Survival in Adult Malignancies.* Their conclusion based on facts collected by world wide research was published in 2004 in Clinical Oncology, Volume 16, pages 549 -560. Under *Abstract,* the following is printed: *"... Results: The overall contribution of curative and adjuvant cytotoxic chemotherapy to 5-year survival in adults was estimated to be **2.3%** in Australia and **2.1%** in the USA. ... Conclusion ... To justify the continued funding and availability of drugs used in cytotoxic chemotherapy, a rigorous evaluation of the cost-effectiveness and impact on quality of life is urgently required. ..."*

Based on this extensive document, it is clear to state that we are loosing *The War on Cancer.* In fact, I believe that based on this Clinical Oncology document it is safe to state that we have actually *lost ground* with our new and improved synthetic, man made chemotherapeutic agents. Granted the 3% in the 1985 was horrific, all our research dollars have resulted in a ***negative*** 33% further decrease in benefit.

Perhaps everyone should contemplate think of chemotherapy as the alternative route?

Both articles are found in their entirety at UtopiaWellness.com, happy reading…

References:

Scientific America (1985) 253(5): 51-59: *The Treatment of Diseases and The War Against Cancer,* by John Cairns

Clinical Oncology (2004) 16: 549-560: *The Contribution of Cytotoxic Chemotherapy to 5-year Survival in Adult Malignancies*, by Graeme Morgan, Robyn Wardy, Michael Bartonz

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Overview

The Contribution of Cytotoxic Chemotherapy to 5-year Survival in Adult Malignancies

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ABSTRACT:
Aims: The debate on the funding and availability of cytotoxic drugs raises questions about the contribution of curative or adjuvant cytotoxic chemotherapy to survival in adult cancer patients.
Materials and methods: We undertook a literature search for randomised clinical trials reporting a 5-year survival benefit attributable solely to cytotoxic chemotherapy in adult malignancies. The total number of newly diagnosed cancer patients for 22 major adult malignancies was determined from cancer registry data in Australia and from the Surveillance Epidemiology and End Results data in the USA for 1998. For each malignancy, the absolute number to benefit was the product of (a) the total number of persons with that malignancy; (b) the proportion or subgroup(s) of that malignancy showing a benefit; and (c) the percentage increase in 5-year survival due solely to cytotoxic chemotherapy. The overall contribution was the sum total of the absolute numbers showing a 5-year survival benefit expressed as a percentage of the total number for the 22 malignancies.
Results: The overall contribution of curative and adjuvant cytotoxic chemotherapy to 5-year survival in adults was estimated to be 2.3% in Australia and 2.1% in the USA.
Conclusion: As the 5-year relative survival rate for cancer in Australia is now over 60%, it is clear that cytotoxic chemotherapy only makes a minor contribution to cancer survival. To justify the continued funding and availability of drugs used in cytotoxic chemotherapy, a rigorous evaluation of the cost-effectiveness and impact on quality of life is urgently required. Morgan, G. *et al*. (2004). *Clinical Oncology* **16,** 549–560

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Key words: Chemotherapy, combined modality treatment, palliation, quality of life, radiotherapy, survival

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Introduction

In adults, cytotoxic chemotherapy became established in the 1970s as a curative treatment in advanced Hodgkin's disease [1], non-Hodgkin's lymphoma [2], teratoma of testis [3] and as an adjuvant treatment for early breast cancer [4].

The initial results suggested the potential use of cytotoxic chemotherapy as a definitive treatment or as an adjuvant therapy in asymptomatic patients with the aim of improving survival. However, as stated by Braverman [5] and others [6–8], the early gains in a few tumour sites have not been seen in the more common cancers. For most patients, the use of cytotoxic chemotherapy is for the palliation of symptoms and to improve quality of life [9], with prolongation of survival being a less important outcome.

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Some practitioners still remain optimistic that cytotoxic chemotherapy will significantly improve cancer survival [10]. However, despite the use of new and expensive single and combination drugs to improve response rates and other agents to allow for dose escalation, there has been no change in some of the regimens used, and there has been little impact from the use of newer regimens. Examples are non-Hodgkin's lymphoma [11] and ovarian cancer [12], in which cyclophosphamide, adriamycin, vincristine and prednisolone (CHOP) and platinum, respectively, (introduced over 20 years ago) are still the 'gold standard' treatment. Similarly, in lung cancer, the median survival has increased by only 2 months during the same time period [13,14], and an overall survival benefit of less than 5% has been achieved in the adjuvant treatment of breast, colon, and head and neck cancers [15–17].

The recent debate on funding of new cytotoxic drugs [18–20] has highlighted the lack of agreement between medical oncologists and funding bodies on the current and

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future value of cytotoxic chemotherapy in cancer management.

In 1986, Kearsley [6] estimated that the contribution of chemotherapy to overall survival in the USA was 4.3%. By reassessing the contribution of definitive and adjuvant cytotoxic chemotherapy to 5-year survival in adult malignancies, we sought to update the estimate in order to provide a more rational basis for the current debate on funding and availability.

Methods

We undertook a literature search for randomised-controlled trials (RCTs) that reported a statistically significant increase in 5-year survival due solely to cytotoxic chemotherapy in adult malignancies (defined as 20 years of age or over). The search period was from 1 January 1990 until 1 January 2004. We searched Medline, Cancerlit and Embase to identify RCTs for each neoplasm using the MeSH headings of chemotherapy, radiotherapy and combined modality treatment. We used the Cochrane Collaboration and the Cochrane Cancer Library to identify meta-analyses and systematic reviews reporting the pooled results of RCTs. We also hand searched reference lists in published papers and other relevant articles.

We accepted the results of the RCTs, meta-analyses or systematic reviews as reported, and did not critically review the data further. As a measure of long-term survival and possible cure, 5-year survival data were used. When 5-year data were not available, shorter survival times were used, provided the outcome reported was statistically significant. We did not attempt to evaluate the effect on cancer outcomes of hormones, immunotherapy, antibodies, tumour vaccines, gene therapy or other novel techniques. Similarly, we did not evaluate the use of cytotoxic chemotherapy for the palliation or non-curative treatment of malignancy, as an impact on 5-year survival was unlikely.

The preferred source of evidence was either a systematic review or a meta-analysis of the RCTs for that malignancy. An RCT could take precedence over a systematic review or meta-analysis, but only when the RCT was from a reputable trials group, more recent than the systematic review or meta-analysis, randomised approximately 1000 patients, and the results were of such a magnitude that data from a previous analysis was clearly inferior.

For each malignancy, the absolute number of individuals obtaining an improvement in 5-year survival as a result of chemotherapy was the product of the number of newly diagnosed cancer patients aged over 20 years with that malignancy, the proportion or subgroup(s) showing a benefit, and the percentage increase in 5-year survival resulting solely from cytotoxic chemotherapy.

For the 22 major malignancies evaluated (Tables 1 and 2), the number of individuals with cancer aged 20 years and over in 1998 were calculated, using the cancer incidence data for Australia from the Australian Institute of Health and Welfare (AIHW) [21] (http://www.aihw.gov.au) and the Surveillance, Epidemiology, and End Results (SEER) data for the USA [22] for 1998.

Malignancies with small total numbers, such as gall bladder, pleura, eye, bone, penis and placenta were excluded. Acute and chronic leukaemia ($n = 1647$ or 2% of total) were not included because of the difficultly in defining outcomes according to FAB (French–American–British) classification and the different outcomes for children and adults. Also, these patients are usually cared for by clinical haematologists rather than medical oncologists. For Australia, the 22 malignancies evaluated were 90% of the total number of newly diagnosed cancer patients for 1998.

In most instances, the contribution to 5-year survival applied to subgroups that varied according to histology, stage, nodal involvement or menopausal status. The size of these subgroups was obtained from data on the distribution of stage in the South Australian Cancer Registry for 1998 [23], from the SEER data for 1998 [22] or from patterns of care studies [24].

The percentage increase in 5-year survival with cytotoxic chemotherapy for the malignancy as a whole or for the subgroup was identified by the literature search as detailed above. Each malignancy was evaluated separately and the absolute number of people to benefit was established. The overall contribution of cytotoxic chemotherapy to 5-year survival was the sum total of the absolute numbers to benefit expressed as a percentage of the total number of cancer patients in the 22 malignancies evaluated.

To establish the general applicability of the data, the contribution to 5-year survival was calculated separately for Australia and the USA. Where assumptions were made, we erred on the side of over-estimating the benefit.

Results

Results are arranged in ICD-9 groupings and are presented in Tables 1 and 2.

Head and Neck Cancer

ICD-9: 140–149, 160, 161; incidence: 2486 (Australia), 5139 (SEER).

Most people with head and neck cancer are treated for cure with radical surgery, radiotherapy, or a combination of both. Three meta-analyses were identified [25–27], which did not show any benefit from adding chemotherapy to radical radiotherapy with or without surgery. A subgroup analysis of a more recent meta-analysis showed a 4% overall improvement in survival with concurrent radiotherapy and chemotherapy [17]. The improvement was restricted to people with extensive disease, and this has been shown separately in advanced glottic cancer [28] and cancer of nasopharynx [29]. The benefit from chemotherapy will only be seen for those with stage III and IV disease. In 1998, this was 63% of the total in Australia and 47% of the total in the USA.

Table 1 − Impact of cytotoxic chemotherapy on 5-year survival in Australian adults

Malignancy	ICD-9	Number of cancers in people aged >20 years*	Absolute number of 5-year survivors due to chemotherapy†	Percentage 5-year survivors due to chemotherapy‡
Head and neck	140−149, 160, 161	2486	63	2.5
Oesophagus	150	1003	54	4.8
Stomach	151	1904	13	0.7
Colon	153	7243	128	1.8
Rectum	154	4036	218	5.4
Pancreas	157	1728	−	−
Lung	162	7792	118	1.5
Soft tissue sarcoma	171	665	−	−
Melanoma of skin	172	7811	−	−
Breast	174	10 661	164	1.5
Uterus	179 + 182	1399	−	−
Cervix	180	867	104	12
Ovary	183	1207	105	8.7
Prostate	185	9869	−	−
Testis	186	529	221	41.8
Bladder	188	2802	−	−
Kidney	189	2176	−	−
Brain	191	1116	55	4.9
Unknown primary site	195−199	3161	−	−
Non-Hodgkin's lymphoma	200 + 202	3145	331	10.5
Hodgkin's disease	201	341	122	35.8
Multiple myeloma	203	1023	−	−
Total		72 903§	1690	2.3%

*Numbers from Ref. [21].
†Absolute numbers (see text).
‡% for individual malignancy.
§Total for Australia 1998 = 80 864 people.

Number benefiting from chemotherapy

Australia: 2486 (incidence) × 63% (subgroup) × 4% (benefit from chemotherapy) = 63 people (2.5%); SEER: 5139 (incidence) × 47% (subgroup) × 4% (benefit from chemotherapy) = 97 persons (1.9%).

Oesophageal Cancer

ICD-9: 150; incidence: 1003 (Australia), 1521 (SEER).

The survival for oesophageal cancer is less than 10% at 5 years [30]. For every 100 newly diagnosed patients, one-third has metastatic disease (M1) at presentation ($n = 33$). In the remainder ($n = 67$), only 40% ($n = 26$) are medically operable, and only 80% of these will have a curative procedure ($n = 21$). Those who do not have an operation ($n = 67 - 21 = 46$) are suitable for treatment by radiotherapy or a combination of chemotherapy and radiotherapy.

In a Cochrane review reporting seven RCTs and 1653 patients [31], preoperative chemotherapy in resectable thoracic cancers was not shown to have a role, but an MRC trial [32] and a recent meta-analysis [33] has confirmed a benefit for preoperative chemotherapy.

A further Cochrane review [34] of combined chemotherapy and radiotherapy compared with radiotherapy alone for oesophageal cancer showed a significant absolute improvement in overall survival at 1 and 2 years for combined chemotherapy and radiotherapy of 9% and 8% respectively, and a 5% absolute reduction in local failure. It can be concluded that, when a non-operative approach was selected, then concomitant chemotherapy and radiotherapy were superior to radiotherapy alone. Chemotherapy, therefore, has a curative role in all patients except those who are M1 at presentation.

Number benefiting from chemotherapy

Australia: 1003 (incidence) × 67% (subgroup) × 8% (benefit from chemotherapy) = 54 people [4.8%]; SEER: 1521 × 67% × 8% = 82 people [4.9%]. This is likely to be an overestimate as data were only available for 2-year follow-up.

Stomach Cancer

ICD-9: 151; incidence: 1904 (Australia), 3001 (SEER).

Stomach cancer has a 22.6−24.8% 5-year survival [30], with surgery being the only established curative procedure. Meta-analyses in 1993 [35] and 1999 [36] suggested that adjuvant chemotherapy might produce a small survival benefit of borderline significance in curatively resected

Table 2 – Impact of cytotoxic chemotherapy on 5-year survival in American adults

Malignancy	ICD-9	Number of cancers in people aged >20 years*	Absolute number of 5-year survivors due to chemotherapy†	Percentage 5-year survivors due to chemotherapy‡
Head and neck	140–149, 160, 161	5139	97	1.9
Oesophagus	150	1521	82	4.9
Stomach	151	3001	20	0.7
Colon	153	13 936	146	1.0
Rectum	154	5533	189	3.4
Pancreas	157	3567	–	–
Lung	162	20 741	410	2.0
Soft tissue sarcoma	171	858	–	–
Melanoma	172	8646	–	–
Breast	174	31 133	446	1.4
Uterus	179–182	4611	–	–
Cervix	180	1825	219	12
Ovary	183	3032	269	8.9
Prostate	185	23 242	–	–
Testis	186	989	373	37.7
Bladder	188	6667	–	–
Kidney	189	3722	–	–
Brain	191	1824	68	3.7
Unknown primary site	195–199	6200	–	–
Non-Hodgkin's lymphoma	200 + 202	6217	653	10.5
Hodgkin's disease	201	846	341	40.3
Multiple myeloma	203	1721	–	–
Total		154 971	3306	2.1%

*Numbers from Ref. [22].
†Absolute numbers (see text).
‡% for individual malignancy.

gastric carcinoma. A further meta-analysis in 2000 [37], restricted to published RCTs only, showed a small survival benefit for adjuvant chemotherapy, but only in patients who had a curative resection.

A recent RCT has shown improvement in survival with chemotherapy and radiotherapy after radical surgery for adenocarcinoma of stomach and gastro-oesophageal junction [38]. At 3.3 years median follow-up, the 3-year overall survival was 52% for combined treatment vs 41% for surgery only. A node-negative D2 surgical resection was required in this RCT for improvement with adjuvant treatment [39].

An American College of Surgeons Patient Care Study for patients treated between 1982 and 1987 found that node-negative D2 surgery was only possible in 31% of people with operable stomach cancer [40]. At presentation, 20% have metastatic disease and 40% of the remainder are locally advanced or inoperable. Chemotherapy, therefore, has a curative role in the 31% out of the 40% who may be candidates for radical surgery (12% of total).

Number benefiting from chemotherapy

Australia: 1904 (incidence) × 40% (operable) × 31% (margin negative) × 11% (overall benefit) × 50% (benefit for chemotherapy) = 13 people (0.7%); SEER: 3001 × 40% × 31% × 11% × 50% = 20 people (0.7%). This is likely to be an overestimate, as data were only available for 3-year follow-up.

Colon Cancer

ICD-9: 153; incidence: 7243 (Australia), 13 936 (SEER).

Surgery is the only established curative treatment for colon cancer, with chemotherapy used as adjuvant treatment. The IMPACT Group analysis in 1995 of three separate trials of 5-fluorouracil and leucovorin in Duke's B and C colon cancer showed an improvement in 3-year disease-free survival of 9% and overall survival benefit of 5% [41]. A further meta-analysis in 1997 compared a no-treatment control with postoperative chemotherapy (excluding liver infusion) in resected colorectal cancer [16]. The overall survival benefit for chemotherapy was 5% for colon cancer and 9% for rectal cancer.

For Duke's B colon cancer, the pooled data of the IMPACT B2 group showed no improvement with adjuvant chemotherapy compared with a no-treatment control [42]. The NSABP pooled analysis of RCTs (C-01, C-02, C-03 and C-04) suggested that people with Duke's B colon cancer benefit from chemotherapy [43]. The analysis

technique has been roundly criticised, and the NSABP conclusions are therefore questionable [44,45].

A meta-analysis of portal-vein chemotherapy in colorectal cancer concluded that a survival advantage of a few percent at 5 years may occur, but an RCT involving several thousand patients would be needed to confirm this [46]. As a benefit for chemotherapy in Duke's B carcinoma has not been established, the benefit from chemotherapy is only in Duke's C colon cancers. This was 35% of the total in Australia and 21% of the total in the USA (SEER).

Number benefiting from chemotherapy

Australia: 7243 (incidence) × 35% (subgroup) × 5% (benefit from chemotherapy) = 128 people (1.8%); SEER: 13 936 × 21% × 5% = 146 people (1.0%).

Rectal Cancer

ICD-9: 154; incidence: 4036 (Australia), 5533 (SEER).

Surgery is the mainstay of treatment, with chemotherapy and radiotherapy used as adjuvant treatments. Two RCTs show that the combination of radiotherapy and chemotherapy decreased local recurrence and increased overall survival compared with a no-treatment control [47,48]. The NSABP R-02 trial [49] showed that chemotherapy alone improved disease-free survival and overall survival, and that radiotherapy alone decreased local recurrence, but had no effect on disease-free survival or overall survival. The improvement in overall survival with chemotherapy alone was 9%, although this was restricted to men. The benefit was in Duke's B and C rectal cancer. This was 60% of the total in Australia and 38% of the total in the USA (SEER).

Number benefiting from chemotherapy

Australia: 4036 (incidence) × 60% (subgroup) × 9% (benefit from chemotherapy) = 218 persons (5.4%); SEER: 5533 × 38% × 9% = 189 persons (3.4%). This may be an overestimate, as the benefit in men (48.7%) was questioned in one study and, like colon cancer, the benefit may only exist for Duke's C cancer.

Anal Cancer

Incidence: about 1% of colorectal cancers; 110 (Australia), 195 (SEER).

The combination of radiotherapy and chemotherapy for sphincter preservation is now standard management, except in advanced disease, in which abdomino-perineal resection is still required after radiotherapy and chemotherapy. In two RCTs [50,51], the addition of chemotherapy to radiotherapy gave a higher complete response rate and colostomy-free survival than radiotherapy alone, but there was no effect on overall survival.

Pancreatic Cancer

ICD-9: 157; incidence: 1728 (Australia), 3567 (SEER).

Pancreatic cancer has a 5-year survival of just over 5% [30]. The impact of gemcitabine is still being evaluated, but a recent RCT showed a median survival of 5.4 months, and a progression-free survival of 2.2 months with gemcitabine alone. An objective response was seen in only 5.6% of patients, and overall survival at 24 months was about 5% [52]. No 5-year data were available.

Lung Cancer

ICD-9: 162; incidence: 7792 (Australia), 20 741 (SEER).

Small-cell lung cancer

Incidence: 19% of total (Australia) and 13% of total in the USA (SEER).

Virtually all patients receive initial cytotoxic chemotherapy. The overall 5-year survival for small-cell lung cancer (SCLC) is 3.5%, or 2.5% in limited-stage disease and 1.2% in extensive-stage disease [53].

Non-small cell lung cancer

In early stage disease, either radical surgery or radical radiotherapy can result in long-term cure. Stage I–IIIA = 21% (Australia); 35% (SEER). A meta-analysis [54] and later a Cochrane review [55] showed that chemotherapy in addition to surgery improves overall survival by 5% at 5 years. Chemotherapy improves survival by 4% at 2 years when given in addition to radiotherapy, and was responsible for a 10% improvement in survival at 1 year compared with best supportive care. A meta-analysis of chemotherapy and radiotherapy compared with radiotherapy alone concluded that chemotherapy provides a mean gain in life expectancy of about 2 months [56]. A further analysis of RCTs of chemotherapy for non-small cell lung cancer has shown an increase in median survival of 2 months over the past 2 decades [13].

Number benefiting from chemotherapy

Australia: SCLC: 7792 (incidence) × 19% (SCLC subgroup) × 3.5% (benefit from CT) = 52 people. NSCLC: 7792 (incidence) × 81% (NSCLC subgroup) × 21% (operable) × 5% (benefit from chemotherapy) = 66 people. Total = 52 + 66 = 118 people [1.5%]; SEER: SCLC: 20 741 × 13% × 3.5% = 94 persons. NSCLC: 20 741 × 87% × 35% × 5% = 316. Total = 410 people (2.0%).

Soft Tissue Sarcoma

ICD-9: 171; incidence: 665 (Australia), 858 (SEER).

Standard care is radical surgery, radiotherapy, or both. Meta-analyses of adjuvant chemotherapy after surgery alone or after postoperative radiotherapy have shown an improvement in time to local and distant recurrence and disease-free survival, but no impact on overall survival

[57,58]. The latest Cochrane review [59] concluded that doxorubicin-based adjuvant chemotherapy seems to improve time to local and distant recurrence. There was a trend towards improved overall survival, but this was not statistically significant.

Malignant Melanoma

ICD-9: 172; incidence: 7811 (Australia), 8646 (SEER).

There is no evidence that cytotoxic chemotherapy improves 5-year survival.

Breast Cancer

ICD-9: 174; incidence: 10 661 (Australia), 31 133 (SEER).

The results of adjuvant chemotherapy have been published in several overview publications. In summary, chemotherapy reduces the rate of recurrence and improves survival for women with early breast cancer [15]. No RCTs have reported results of adjuvant chemotherapy in women aged 70 years or over, and any benefit in this age group is therefore not evidence based.

The absolute survival benefit at 5 years for chemotherapy in women less than 50 years is 6.8% for node-positive and 3% for node-negative women. For women aged between 50 and 69 years, the absolute survival benefit at 5 years is 2.1% for node-positive and 3.9% for node-negative women. A more recent RCT [60] has shown that a benefit from adjuvant chemotherapy in node-negative women aged 50–69 years is limited to women with receptor-negative disease; only 30% of node-negative women are in this group.

An analysis of surgical management of invasive breast cancer in Australia in 1995 [24] showed that 85% of women presented with early disease and 15% with advanced disease. Overall, 64% of women were node negative. Of the 10 661 women with a new diagnosis of breast cancer in Australia in 1998, 2696 women were less than 50 years and 4998 women were between 50 and 70 years. SEER data for 1998 [22] show that for women less than 50 years, 4748 were node negative and 2706 node positive. For women aged 50–70 years, 9389 were node negative and 4199 were node positive.

Number benefiting from chemotherapy

Australia: less than 50 years; node negative: 2696 (incidence) $\times$ 85% (operable) $\times$ 64% (node-negative subgroup) $\times$ 3% (benefit from chemotherapy) = 44 women. Node positive: 2696 (incidence) $\times$ 85% (operable) $\times$ 36% (node-positive subgroup) $\times$ 6.8% (benefit from CT) = 56 women. Aged 50 to 69 years: node negative: 4998 (incidence) $\times$ 85% (operable) $\times$ 64% (node negative) $\times$ 30% (ER negative) $\times$ 3.9% (benefit from chemotherapy) = 32 women. Node positive: 4998 (incidence) $\times$ 85% (operable) $\times$ 36% (node positive) $\times$ 2.1% (benefit from chemotherapy) = 32 women. Total = 164 (1.5%); SEER: less than 50 years: node negative: 4784 $\times$ 85% $\times$ 3% = 122 women; node positive: 2706 $\times$ 85% $\times$ 6.8% = 156 women. Aged 50–69 years: node negative: 9389 $\times$ 85% $\times$ 30% $\times$ 3.9% = 93 women. Node positive: 4199 $\times$ 85% $\times$ 2.1% = 75 women. Total = 446 (1.4%).

Uterine Cancer

ICD-9: 179 + 182; incidence: 1399 (Australia), 4611 (SEER).

There is no evidence that cytotoxic chemotherapy improves 5-year survival.

Cervix Cancer

ICD-9: 180; incidence: 867 (Australia), 1825 (SEER).

A meta-analysis [61], later a Cochrane Review [62], has confirmed a 12% absolute overall survival benefit with concurrent radiotherapy and chemotherapy compared with surgery alone or radiotherapy alone. There was statistical heterogeneity for outcomes, with a greater benefit for trials with a high proportion of stage I and II women.

Number benefiting from chemotherapy

Australia: 867 (incidence) $\times$ 12% (benefit from chemotherapy) = 104 women (12%); SEER: 1825 $\times$ 12% = 219 women (12%).

Ovarian Cancer

ICD-9: 183; incidence: 1207 (Australia), 3032 (SEER).

Several meta-analyses have been published [63–67]. The latest Cochrane review [68] concludes that 'the available evidence, although not conclusive, suggests that platinum-based chemotherapy is better than non-platinum therapy; that combination therapy improves survival compared with platinum alone; and no difference in effect has been shown between cisplatin and carboplatin'.

The ICON2 trial [69] reported no improvement in survival with cyclophosphamide, doxorubicin and cisplatin compared with single-agent carboplatin. The trial was stopped early due to the better response rates with the new drug paclitaxel and the ICON3 trial was undertaken. This has shown no difference between the test arm of paclitaxel and carboplatin and either of the two control arms: carboplatin alone or cyclophosphamide, doxorubicin and cisplatin [12].

Although response rates may have increased, there is no evidence that chemotherapy has improved overall 5-year survival since 1980 when platinum was standard treatment. Any improvement in overall survival in 2004 is therefore likely to be due to improvements in surgery, multidisciplinary clinics, or both.

An RCT published in the early 1980s showed that cisplatin, chlorambucil, or a combination of both, produced a 5-year survival benefit of 11% in women with advanced ovarian cancer [70]. The FIGO II–IV subgroup comprises 79% of the total (Australia) or 74% of the total (SEER).

Number benefiting from chemotherapy

Australia: 1207 (incidence) × 79% (subgroup) × 11% (benefit from chemotherapy) = 105 women (8.7%); SEER: 3302 × 74% × 11% = 269 women (8.9%).

Prostate Cancer

ICD-9: 185; incidence: 9869 (Australia), 23 242 (SEER).

There was no evidence that cytotoxic chemotherapy improves 5-year survival.

Testis Cancer

ICD-9: 186; incidence: 529 (Australia), 989 (SEER).

Seminoma of testis

Incidence: 529 × 50% of total = 265 (Australia); 989 × 59% of total = 584 (SEER).

A review article [71] concluded that chemotherapy only has a role in bulky disease with para-aortic masses over 5 cm diameter or in those who relapse after definitive radiotherapy. These patients are in the minority of those with seminoma of testis — maximum 20%.

Non-seminomatous testicular cancer

Incidence: 529 × 50% of total = 265 (Australia); 989 × 41% of total = 405 (SEER).

The outcome was changed dramatically by the use of cisplatinum [4]. The introduction of effective chemotherapy was not due to an RCT, but the results were a major improvement on previous treatment. Nowadays, up to 95% are long-term disease-free survivors, although this is less in those presenting with poor prognostic grouping. In stage I non-seminomatous testicular cancer (NSTC) (40% total), a 'surveillance' policy is standard practice, and only the 20% of this group who relapse will receive chemotherapy.

Number benefiting from chemotherapy

Australia: seminoma: 265 (incidence) × 20% (relapse) × 95% (benefit from chemotherapy) = 50; NSTC: stage I = 265 (incidence) × 40% (subgroup) × 20% (relapse) × 95% (benefit from chemotherapy) = 20; stage II−IV = 265 (incidence) × 60% (subgroup) × 95% (benefit from chemotherapy) = 151; total = 221 (41.8%). SEER: seminoma: 584 × 20% × 95% = 111; NSTC: stage I = 405 × 40% × 20% × 95% = 31; stage II−IV = 405 × 60% × 95% = 231; total = 373 (37.7%).

Bladder Cancer

ICD-9: 188; incidence: 2802 (Australia), 6667 (SEER).

Meta-analyses of neoadjuvant chemotherapy in locally advanced bladder cancer have been published [72,73]. The first, in 1995, stated that insufficient information was available and that chemotherapy could not be recommended for routine use. The second, in 2000, came to the same conclusion, but commented that, although an additional four RCTs had been completed, none had been published in full. The MRC-EORTC randomised trial [74] showed a non-significant survival benefit for chemotherapy of 5.5%, and an increase in median survival at 3 years of 8.5 months. No data were available for 5-year survival. A further RCT has shown a benefit for neoadjuvant chemotherapy and cystectomy compared with cystectomy alone [75]. A further meta-analysis showed a 5% absolute benefit at 5 years, but this was not statistically significant [76].

Number benefiting from chemotherapy

Although there may be a trend towards improved overall survival, this has not been shown to be statistically significant.

Kidney Cancer

ICD-9: 189l; incidence: 2176 (Australia), 3722 (SEER).

There was no evidence that cytotoxic chemotherapy improves 5-year survival.

Brain Cancer

ICD-9: 191; incidence: 1116 (Australia), 1824 (SEER).

A meta-analysis in 1993 suggested that chemotherapy was 'advantageous' and should be standard practice [77]. The conclusions were criticised because several published trials had been omitted and the dose of radiotherapy was suboptimal in several trials, having been reduced to allow for chemotherapy to be given [78]. A later meta-analysis of the use of multidrug or single-agent chemotherapy showed a 22% decrease in 1-year survival for multi-agent chemotherapy compared with single agent [79]. A recent Cochrane review [80] showed an absolute survival benefit of 6% for chemotherapy at 1 year, but gave no evidence of any benefit at 5 years. Analysis was confined to high-grade glioma: 82% of total (Australia); Grade II−IV 62% (USA). We have not evaluated outcome in other adult cerebral tumours.

Number benefiting from chemotherapy

Australia: 1116 (incidence) × 82% (subgroup) × 6% (benefit from chemotherapy) = 55 (4.9%); SEER: 1824 × 62% × 6% = 68 (3.7%). This is likely to be an overestimate, as only 1-year data are available.

Carcinoma of Unknown Primary Site

ICD-9: 195−199; incidence: 3161 (SEER), 6200 estimate (USA).

Most patients receive chemotherapy with essentially palliative intent [81,82]. Although 5-year survival in Australia is 13.4% for men and 11.5% for women, there is no evidence that chemotherapy is better than best supportive care plus placebo.

Hodgkin's Disease

ICD-9: 201; incidence: 341 (Australia), 846 (SEER).

Early stage disease: (I or IIA): incidence: 341 × 68% of total = 232 (Australia), 846 × 61% of total = 516 (SEER).

Radiotherapy has been the standard treatment, although there is now a move to combine chemotherapy and radiotherapy to minimise long-term complications. In a meta-analysis of the initial treatment of early stage Hodgkin's disease [83], the addition of chemotherapy to radiotherapy, or the use of more extensive radiotherapy fields, had a large effect on relapse, but only a small effect on overall survival. If initial treatment had been radiotherapy alone, many recurrences could be salvaged with chemotherapy alone or with bone-marrow transplantation. This represents an improvement in 5-year survival to 95% from 80% with radiotherapy alone.

Advanced disease (IIB–IV): incidence: 341 × 32% of total = 109 (Australia), 846 × 39% of total = 330 (SEER).

Chemotherapy is the established treatment [1]. In stage IIB–IV, Hodgkin's disease chemotherapy results in an 80% 5-year overall survival, including those receiving bone-marrow transplantation [84].

Number benefiting from chemotherapy

Australia: stage I–IIA = 232 (incidence) × 15% (benefit from chemotherapy) = 35; stage IIB–IV = 109 (incidence) × 80% (benefit from chemotherapy) = 87; total = 122 (35.8%); SEER: stage I–IIA = 516 × 15% = 77; stage IIB–IV = 330 × 80% = 264; total = 341 (40.3%).

Non-Hodgkin's Lymphoma

ICD-9: 200 + 2002; incidence: 3145 (Australia), 6217 (SEER).

Low-grade non-Hodgkin's lymphoma (NHL) is a heterogeneous group characterised by a long clinical course, with median survivals between 3 and 8 years. In stage I or II, radiotherapy often achieves long-term survival; the addition of chemotherapy does not improve survival. For stage III and IV, treatment is controversial and may involve conservative management with no treatment unless B symptoms are present or if there is disease progression. More intensive chemotherapy does not improve overall survival. With intermediate and high-grade NHL, the use of chemotherapy has improved the prognosis by inducing durable complete remission in a significant proportion of patients. However, this benefit is restricted to NHL patients with large B cell histology (30% total), where about 50% of the 70% who obtain a complete response are durable long-term survivors.

Number benefiting from chemotherapy

Australia: 3145 (incidence) × 30% (subgroup) = 944; complete response = 944 × 70% = 661; overall survival = 661 × 50% = 331 (10.5%); SEER: 6217 × 30% × 70% × 50% = 653 (10.5%).

Multiple myeloma

ICD-9: 203; incidence: 1023 (Australia), 1721 (SEER).

There is no doubt that chemotherapy and radiotherapy provide good symptom control and improve quality of life. However, a meta-analysis [85] of combination chemotherapy or melphalan plus prednisone has shown no difference in mortality, either overall or within any subgroup. There is no evidence that chemotherapy has an impact on survival.

Discussion

The 5-year relative survival rate for cancer patients diagnosed in Australia between 1992 and 1997 was 63.4% (95% CI, 63.1–63.6) [30]. In this evidence-based analysis, we have estimated that the contribution of curative and adjuvant cytotoxic chemotherapy to 5-year survival in adults is 2.3% in Australia and 2.1% in the USA (Tables 1, 2).

These estimates of benefit should be regarded as the upper limit of effectiveness, as some eligible patients do not receive cytotoxic chemotherapy because of age, poor performance status or patient choice. Also, as noted in the text, the benefit of cytotoxic chemotherapy may have been overestimated for cancers of oesophagus, stomach, rectum and brain.

There are differences in stage distribution and cancer incidence between and within countries. However, any variation would need to be extremely large to have a major effect on the estimated percentage likely to benefit. This is demonstrated by the small effect on the survival benefit of the different proportions of Duke's C colon cancer reported in Australia and the USA (35% and 21%, respectively).

The similarity of the figures for Australia and the USA strongly suggest that a benefit of less than 2.5% is likely to be applicable in other developed countries.

For outcome data, we relied on a systematic review or a meta-analysis of RCTs of treatment outcomes rather than an individual RCT. This methodology was used to reduce the bias inherent in only presenting the results from a single positive RCT, while ignoring data from a number of negative RCTs on the same subject. Likewise we did not accept the views published by 'expert groups'. As an example, the promotion by NICE of taxanes for ovarian cancer [86] was not substantiated by ICON3 [12] or supported by another Health Technology Assessment group [87], and was later reversed [88].

Overall, only 13 out of the 22 malignancies evaluated showed any improvement in 5-year survival, and the improvement was greater than 10% in only three of those 13 malignancies. The five most 'chemo-sensitive' cancers, namely testis, Hodgkin's disease and non-Hodgkin's lymphoma, cervix and ovary, accounted for 8.4% of the total incidence in Australia in 1998. In this group, the 5-year survival rate due solely to cytotoxic chemotherapy was 14%.

The five most common adult malignancies (colorectal, breast, prostate, melanoma and lung cancer) accounted for 56.6% of the total incidence in Australia in 1998. In this

group, the 5-year survival rate due solely to cytotoxic chemotherapy was 1.6%.

The minimal impact on survival in the more common cancers conflicts with the perceptions of many patients who feel they are receiving a treatment that will significantly enhance their chances of cure. In part, this reflects the presentation of results as a 'reduction in risk' rather than as an absolute survival benefit [89,90] and by exaggerating the response rates by including 'stable disease'.

The best example of the 'over-selling' of chemotherapy is in breast cancer, where chemotherapy was introduced as the example of the new cure for solid malignancies. In Australia, in 1998, only 4638 of the 10 661 women with newly diagnosed breast cancer were eligible for adjuvant chemotherapy (44% of total). From our calculations, only 164 women (3.5%) actually had a survival benefit from adjuvant chemotherapy. In other words, on average, 29 women had to be treated for one additional woman to survive more than 5 years.

Notwithstanding, several studies have justified adjuvant chemotherapy in early breast cancer by showing that women are willing to undertake treatment for a very small benefit [91].

This does not apply to all malignancies. In lung cancer, an analysis of how patients value the trade-off between the survival benefit of chemotherapy and its toxicities showed that the willingness to accept chemotherapy as a treatment varied widely [92]. Some patients would have chemotherapy for a likely survival benefit of 1 week, and others would not choose chemotherapy for a benefit of 24 months. Others would not choose chemotherapy for any survival benefit, but would do so for an improvement in quality of life. The paper also found that some patients would not have chosen chemotherapy if they had been more fully informed.

Despite new and improved drugs, combinations and additional agents to allow for dose escalation and to prevent drug-induced emesis and neutropenic sepsis, there has been little change in the regimens used to treat 'chemo-sensitive' cancers. Examples are non-Hodgkin's lymphoma [11] and ovarian cancer [12], where CHOP and platinum, respectively, both introduced over 20 years ago, are still the 'gold standard'.

Other innovations, such as bone-marrow transplantation for breast cancer, have shown no benefit [93,94]. Similarly, the addition of anthracyclines and taxanes to adjuvant treatment of breast cancer is only likely to improve survival in the subgroups treated by an estimated 1%, but at the risk of cardiac toxicity [95] and neurotoxicity [86]. Also, recent studies have documented impaired cognitive function in women receiving adjuvant treatment for breast cancer [96], and the suggestion raised in 1977 [97] that adjuvant chemotherapy was merely a toxic means of achieving an oophorectomy is still unresolved [98].

Our analysis does not address the effectiveness or survival contribution of cytotoxic chemotherapy in the palliative or non-curative treatment of malignant disease, but the value of palliative chemotherapy has been questioned [99,100].

In breast cancer, the optimal regimen(s) for cytotoxic chemotherapy in recurrent/metastatic disease are still not defined, despite over 30 years of 'research' and a plethora of RCTs since the original Cooper regimen was published in 1969 [101]. There is also no convincing evidence that using regimens with newer and more expensive drugs are any more beneficial than the regimens used in the 1970s [102].

In addition, two systematic reviews of chemotherapy in recurrent or metastatic breast cancer have not been able to show any survival benefit [103,104]. The absence of quality-of-life data in many RCTs of cytotoxic chemotherapy has also been noted [105].

Although guidelines may exist for some uses of palliative cytotoxic chemotherapy, clinicians are not restricted from giving second, third or fourth line palliative chemotherapy in the face of progressive disease and minimal response rates. Although response rates below 15% may be due solely to a placebo effect [106,107], this fact has not been openly addressed. Indeed the whole question of the validity of response rates is very much open to debate [108,109].

This, of course, leads to a discussion of the cost implications of cytotoxic chemotherapy. Although this is a separate issue, we note that the cost of cytotoxic drugs provided by the Pharmaceutical Benefits Scheme in Australia increased from $67M for the year ended 30 June 2000 to $101.3M for the year ended 30 June 2001 [110]. The 51% increase in total drug cost was due to a 17% increase in the number of prescriptions and a 29% increase in average prescription price.

In view of the minimal impact of cytotoxic chemotherapy on 5-year survival, and the lack of any major progress over the last 20 years, it follows that the main role of cytotoxic chemotherapy is in palliation. Although for many malignancies, symptom control may occur with cytotoxic chemotherapy, this is rarely reported and, for most patients, the survival in those who obtain a response is rarely beyond 12 months.

The introduction of cytotoxic chemotherapy for solid tumours and the establishment of the sub-speciality of medical oncology have been accepted as an advance in cancer management. However, despite the early claims of chemotherapy as the panacea for curing all cancers, the impact of cytotoxic chemotherapy is limited to small subgroups of patients and mostly occurs in the less common malignancies.

Even so, any new chemotherapy drug is still promoted as a major breakthrough in the fight against cancer, only to be later rejected without the fanfare that accompanied its arrival.

In an environment of scarce resources and cost-containment, there is a need for evidence-based assessment before any new or previously accepted treatment is accepted as standard practice. To justify the continued funding and availability of drugs used in cytotoxic chemotherapy, a rigorous evaluation of the cost-effectiveness and impact on quality of life is urgently required.

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The Treatment of Diseases and the War against Cancer

To judge the progress in the war against cancer one must understand the role of trial and error in the evolution of medicine and know something about the natural history of the commoner forms of cancer

by John Cairns

Cancer is a disease that will touch most of us, directly or indirectly. One in three Americans gets cancer at some time in his or her life, and one in five dies of it. This article measures the progress that has been made in the treatment of cancer. Because it is a rather controversial subject, I describe how such judgments are made and what sources of information are available. Before discussing cancer, it is useful to consider briefly the problem of developing a treatment for any disease.

The molecular biology of all living creatures shows an underlying unity, even though the particular form of each species reflects chance events in its evolutionary history. We can be confident that any newly discovered animal will prove to have the same kinds of informational macromolecules and the same genetic code as other forms of life, but even if we were given a complete description of the animal's habitat, we could not predict exactly what the animal would look like because that would depend on the history of its ancestors. Still less could we predict the animal's diseases. For example, who could have guessed that *Homo sapiens* would share with the humble guinea pig the unenviable distinction of being incapable of synthesizing ascorbic acid or share with armadillos a susceptibility to the bacterium that causes leprosy, or that intestinal cancer usually occurs in the large intestine of humans and in the small intestine of sheep?

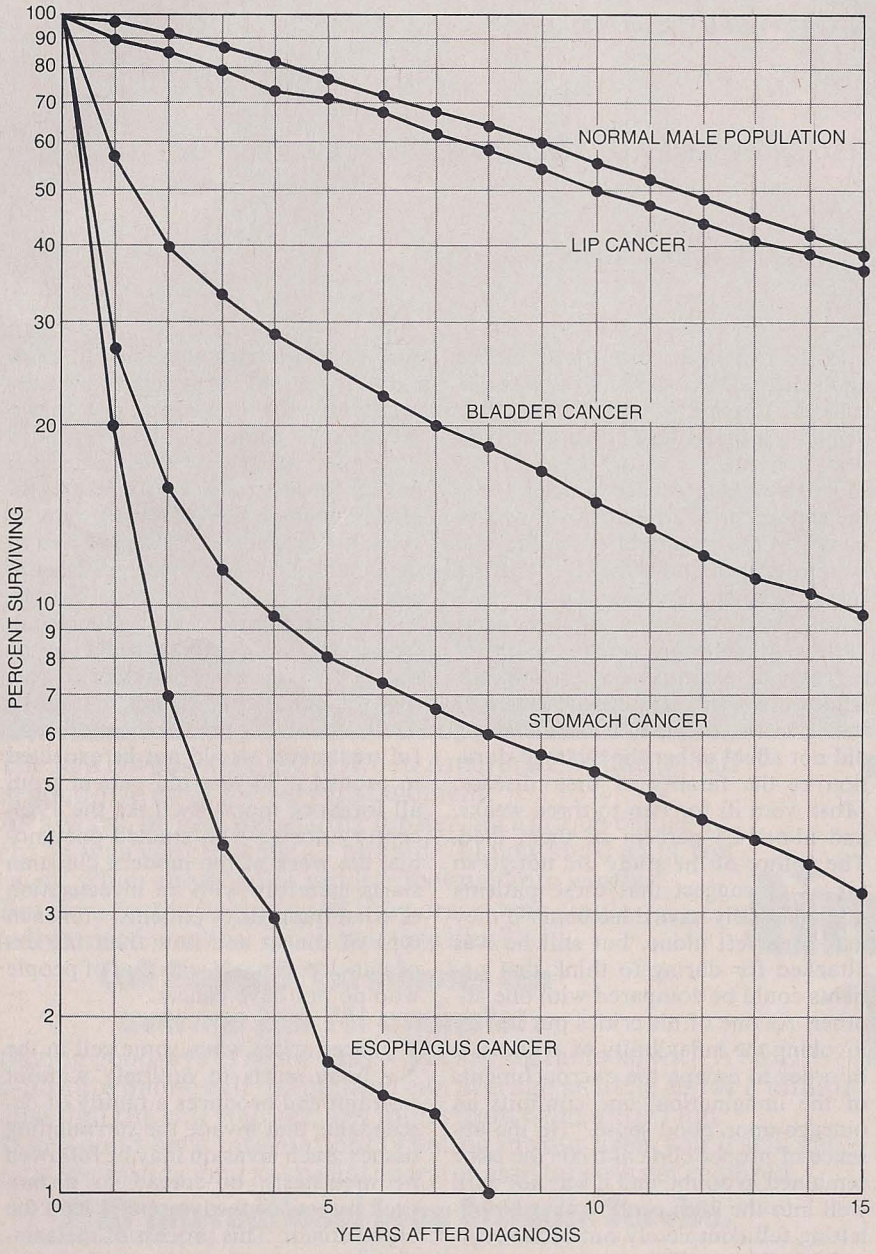
If we cannot predict the existence and salient characteristics of each disease, we certainly have no basis for deciding a priori how diseases should best be treated. It would seem to be a short step, therefore, to conclude that the treatment of diseases ought to be based on the results of some rational system of trial and error. Yet this is a rather new idea in the annals of medicine. For example, a famous early 19th-century comparison of the fate of a group of patients with pneumonia, who were bled at various stages of their disease, showed that bloodletting did not affect either the average duration or the fatality of their disease. Most were ill for two to three weeks, and about 25 percent of them died. The author of the study did not go so far as to suggest that these patients might actually have done better if they had been left alone, but still he was attacked for daring to think that patients could be compared with one another. As one of his critics put it, "By invoking the inflexibility of arithmetic in order to escape the encroachments of the imagination, one commits an outrage upon good sense." (In the absence of proper clinical trials the issue remained in doubt, and it was not until well into the 20th century that bloodletting fell completely out of favor.)

With diseases such as pneumonia or cancer, which are sometimes fatal and sometimes not, there may be no way of determining whether any particular patient's survival was predestined or should be attributed to the treatment. And so it becomes necessary to compare the response of groups of patients rather than the response of one or two individuals. Some 100 different kinds of human cancer are recognized. Each has its characteristic behavior that includes average age of onset, rate of growth and tendency to spread and to be lethal. Each must therefore be considered as if it were a separate disease. Furthermore, most cancer patients are already well into middle or old age, so that some way must be found to correct for other, "competing" causes of death. After all, even the most successful treatments would not be expected to protect a 90-year-old patient from all forms of mortality. Like the 19th-century doctor who studied pneumonia, the work of the modern clinician starts therefore with an investigation of what happens to patients with each type of cancer and how their life expectancy compares with that of people who do not have cancer.

Cancer arises when some cell in the body starts to multiply without restraint and produces a family of descendants that invade the surrounding tissues. Such invasion may be followed by metastasis, or spread to distant sites, by way of the lymphatics and the bloodstream. This process of metastasis is the main reason for the lethality of cancer, because it puts the disease beyond the reach of surgery and local irradiation. Some cancers, for reasons not known, are incapable of metastasis (for example, most forms of skin can-

cer). These cancers are easily dealt with, unless of course the process of local invasion is itself lethal (as it can be, particulary in certain forms of brain cancer). At the other extreme, the normal cells of the bone marrow and lymphatic system are already programmed to move around the body, and so it is not surprising that cancers arising among these cells (the leukemias and lymphomas) are likely to be disseminated throughout the body from the start. Most forms of cancer lie between these extremes.

Although it has recently become possible to study directly the changes in gene structure and function found in certain cancer cells [see "A Molecular Basis of Cancer," by Robert A. Weinberg; SCIENTIFIC AMERICAN, November, 1983], we still know little about what controls the multiplication and territorial restraints of most cells and tissues. For the time being, therefore, our knowledge of the behavior and prognosis of each type of cancer remains largely empirical. Over the past century pathologists have built up a classification of human cancers according to the origin and category of cell involved, and they have further subdivided each type of cancer according to the appearance of the cells and their general growth pattern. This classification is important because the different cancers behave in very different ways. Some tend to be rapidly fatal and some are not; most kinds occur predominantly in old age but a few occur only in children; some are common and some are rare; some are common in rich nations and rare in poor ones, and for others the reverse is true.

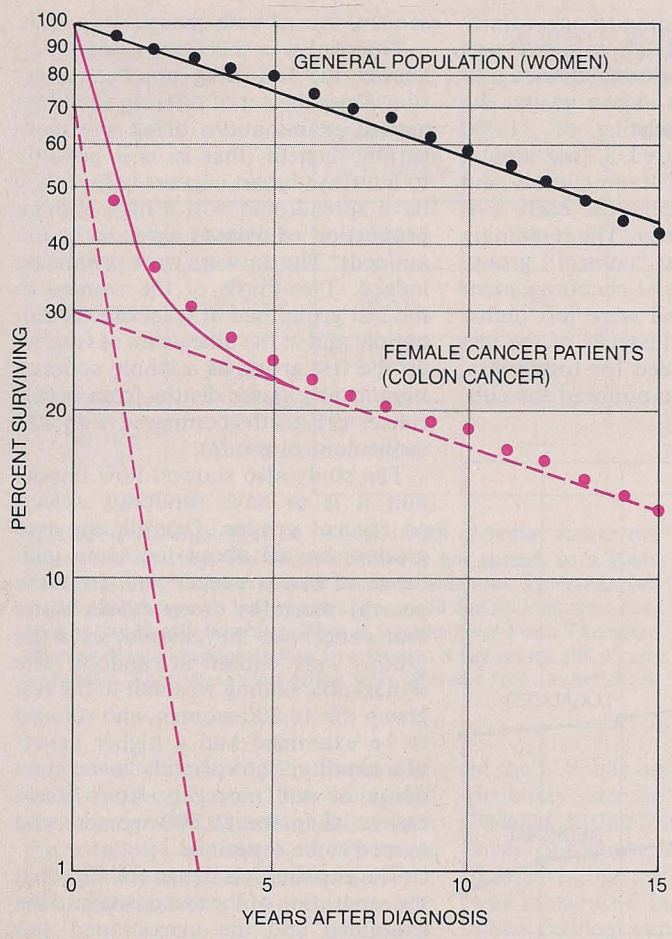


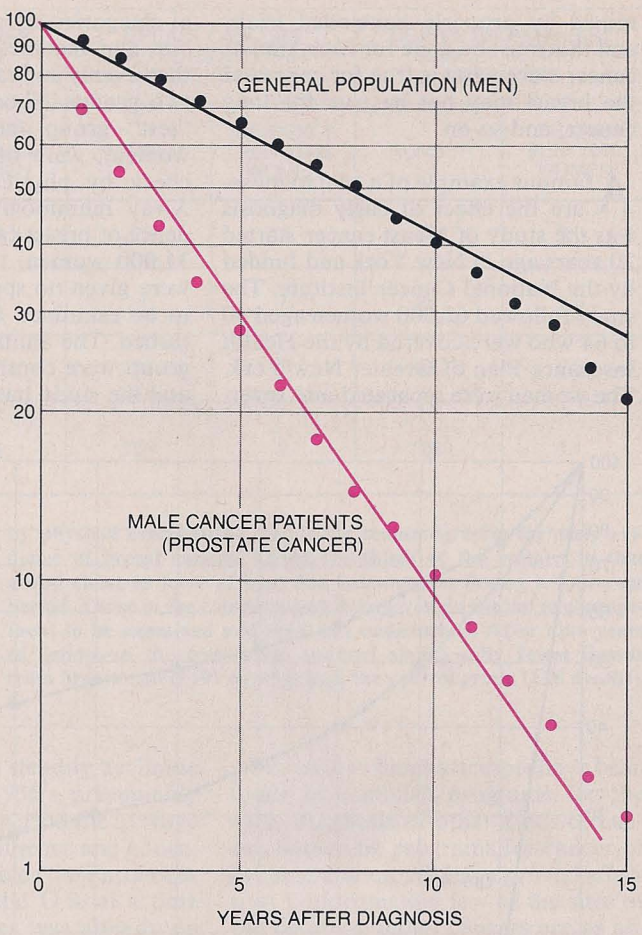
SURVIVAL OF NORWEGIAN MEN who had various types of cancer is compared with the survival of similarly aged males in that nation's population as a whole. In the years after diagnosis lip cancer caused a negligible decrease in life expectancy, whereas cancer of the esophagus was nearly always rapidly fatal. The survival rates for patients who had cancers of the bladder and the stomach fell somewhere between those extremes. The statistics cover the years from 1953 through 1964 and come from the Cancer Registry of Norway.

Since World War II cancer registries have been set up in several states and nations to record the changing trends in cancer incidence and mortality. The records collected by some of these registries yield a rather precise picture of the natural history of cancer, and that is the necessary starting point for any discussion of treatment. The Cancer Registry of Norway has published its findings in book form and is therefore a particulary accessible source. Norway has a population of about 3.5 million, and the registry has followed the fate of the 200,000 cancer cases diagnosed there since 1953. As a sample of these statistics, the illustration at the left shows the pattern of survival of men with four kinds of cancer, chosen to demonstrate how differently various cancers behave. At some sites, such as the lip, cancer is associated with a negligible decrease in life expectancy; at other sites, such as the esophagus, it is nearly always rapidly fatal.

A group of patients can be considered cured of their cancers if they die at about the same rate as the general population, which they would if, thanks to their treatment, they had been returned to the common pool. The essential step, therefore, in determining how often a particular type of cancer can be cured or controlled is to estimate from statistics what fraction of cancer patients die at the same age as they would have died if they had not had the cancer (that is, what fraction are dying from causes unrelated to their cancer). The survival rate of Norwegian women who have colon cancer, for instance, has been compared with the survival rate of the general population of women characterized by the same age distribution. Most of the patients die rather soon after diagnosis, but a sizable minority, about 30 percent, die at the same rate as the general population (that is, behave as if they have been cured). That is what we would expect if some of the patients die of their cancer and some do not.

The Norwegian registry lists 40 major sites of cancer for males and 43 for females. Similar calculations can be made for each site. By summing the estimates I calculate that about 25 per-





CANCER PATIENTS are considered cured if they die at about the same rate as the general population. The graph at the top left compares the survival rate of Norwegian women who had colon cancer (*colored dots*) to the survival rate of the general population of women who had the same age distribution (*black dots*). The solid gray line shows that the general population had a half-life of about 13 years. (A half-life is the time required for half of a given population to die.) The solid colored line is the summation of the two broken lines and shows that the women with colon cancer can be considered to fall into one of two categories: 70 percent had a half-life of eight months and 30 percent had a half-life of 13 years. In other words, a subgroup consisting of 30 percent of the women died at the same rate as the general population. Some cancers, on the other hand, show no such subgroup and in this sense should perhaps be considered incurable by present methods. Cancer of the prostate is one example; the graph at the top right compares the survival rate of Norwegian men who had prostate cancer (*colored dots*) to the survival rate of similarly aged men in the general population (*black dots*). The solid gray line shows that the general population had a half-life of eight years, the solid colored line that the cancer patients had a half-life of three years. About a third of these cancer patients suffered no loss of life span as a result of their disease.

cent of all male cancer patients and about 40 percent of all female cancer patients died of causes unrelated to their cancer. In other words, about a third of all Norwegian cancer patients suffered no loss of life span as the result of their disease.

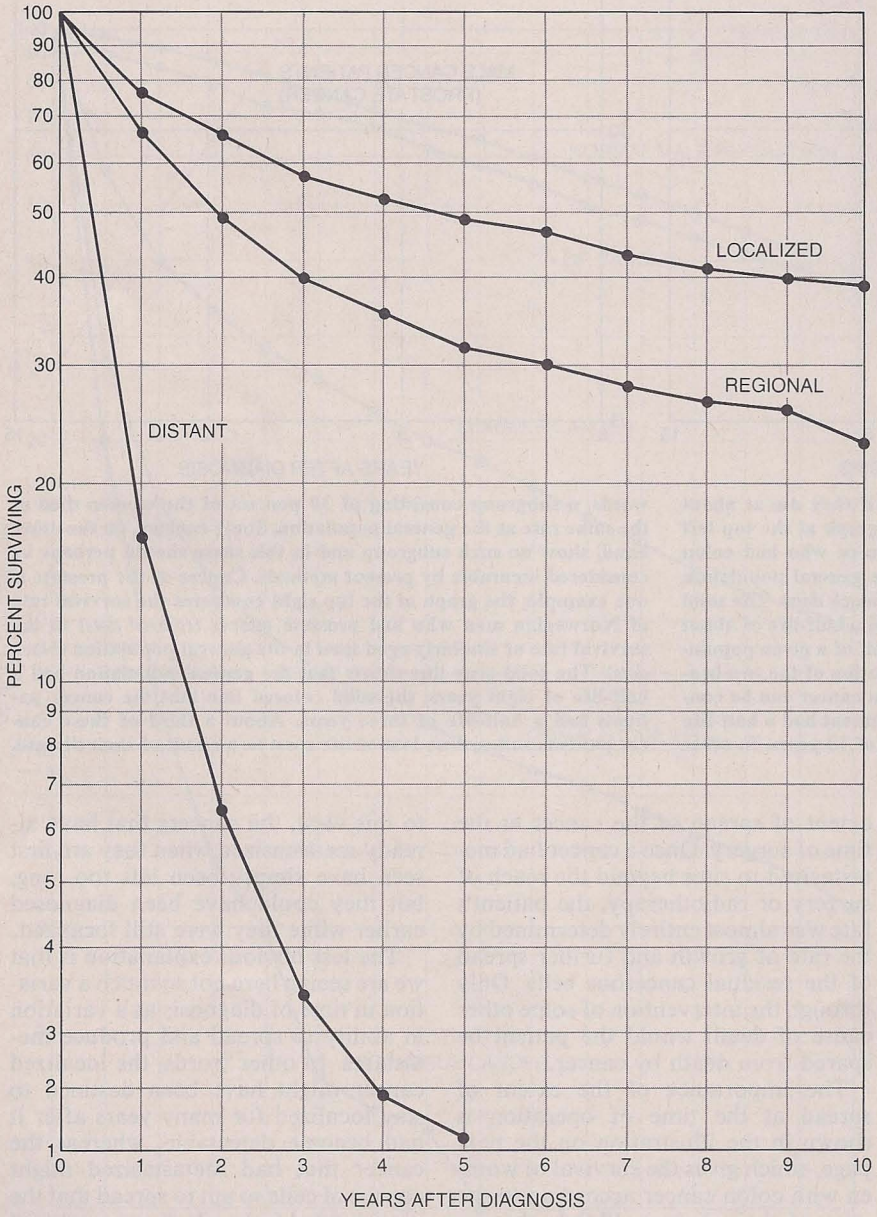
In these statistics from the 1950's and 1960's we are looking at the results of treatment by surgery, occasionally backed up by X-irradiation when the primary tumor was inaccessible to surgery. It is the picture of what used to happen before the advent of screening programs, chemotherapy and numerous clinical trials. The major ancillary aids to surgery, such as blood transfusion, antibiotics and improved forms of anesthesia, had been developed and disseminated by the early 1950's, so that the deciding issue, for nearly every patient, had by then become the extent of spread of the cancer at the time of surgery. Once a cancer had metastasized to sites beyond the reach of surgery or radiotherapy, the patient's fate was almost entirely determined by the rate of growth and further spread of the residual cancerous cells. Only through the intervention of some other cause of death would the patient be spared from death by cancer.

The importance of the extent of spread at the time of operation is shown in the illustration on the next page, which gives the survival of women with colon cancer according to the state of their disease. Plainly the patients' chances were least good if their cancer had already spread when it was first diagnosed. There are, however, two possible explanations for this effect. The first and more obvious interpretation is that the crucial determinant is the time of diagnosis; according to this view, the cancers that have already metastasized when they are first seen have simply been left too long, but they could have been diagnosed earlier while they were still localized.

The less obvious explanation is that we are seeing here not so much a variation in time of diagnosis as a variation in ability to spread and produce metastases. In other words, the localized cancer might have been destined to stay localized for many years after it had become detectable, whereas the cancer that had metastasized might consist of cells so apt to spread that the cancer would already have produced metastases when it was very small and still undetectable. If the first explanation is the correct one, earlier diagnosis could bring great benefit; if the second is correct, there might be negligible benefit. The actual benefits of earlier diagnosis must therefore be deter-

mined by properly controlled trials, and this must be done for each kind of cancer since what is true for cancer of the breast may not be true for lung cancer, and so on.

A famous example of a trial to measure the effect of early diagnosis was the study of breast cancer started 20 years ago in New York and funded by the National Cancer Institute. The study followed 62,000 women aged 40 to 64 who were covered by the Health Insurance Plan of Greater New York. The women were separated into several categories according to age, family size and income. Each category was then evenly and randomly divided into two groups. Those in one group, the "test" group (consisting of 31,000 women), were offered a free annual check by physical examination and X-ray mammography for early evidence of breast cancer. The remaining 31,000 women, the "control" group, were given no special encouragement to be examined and were left undisturbed. The annual checks of the test group were continued for four years, and the study has monitored the subsequent fate of both groups since then.



EXTENT OF METASTASIS, or spread, of a cancer has a large impact on the chance of long-term survival after diagnosis. The data shown here are from a study of Norwegian women between the ages of 55 and 74 who were diagnosed as having cancer of the colon. In some of the patients (*top curve*) the cancer was localized in the gut wall, and two-thirds of these women appear to have suffered no loss of life expectancy. When the cancer was seen to have spread to the local lymph glands (*middle curve*), only a third of the patients had a normal life expectancy. When the cancer was seen to have undergone metastasis to distant sites (*bottom curve*), the prospects for long-term survival were most unfavorable.

The trial was therefore designed to answer the following practical question: Does the act of offering such free annual examinations bring any measurable benefit (that is, is it possible to intercept breast cancers before they have spread, and will a high enough proportion of women agree to be examined)? The answers were promising indeed. Two-thirds of the women in the test group had at least one examination, and in the nine years of follow-up the test group as a whole suffered significantly fewer deaths from breast cancer (91 deaths compared with 128 in the control group).

The study also showed how important it is to have randomly selected control groups. Overall, the two groups showed about the same incidence of breast cancer and the same general mortality from causes other than cancer—as they should, since the groups were chosen at random. The remarkable finding was that in the test group the 10,200 women who refused to be examined had a higher general mortality, but a slightly lower incidence of and mortality from breast cancer, than the 20,800 women who agreed to be examined.

The explanation lies in the fact that the separation of the test group into the examined and the unexamined was the result of self-selection. The women who refused to be checked were less interested in their health and proved to have a lower level of education than the women who agreed to be checked. Because breast cancer is commoner among the well-educated than it is among the indigent and less-educated, these differences between the two self-selected categories of women are actually not surprising. There is therefore an important lesson to be learned here. If the comparison had been simply between the women who were examined and those who refused to be, the study could have reached the ludicrous conclusion that annual examination for the early signs of breast cancer lowers general mortality and slightly raises mortality from the very disease the exercise is designed to prevent. But because a randomly selected control was included, the study produced a reliable estimate of the actual benefits of screening for breast cancer.

To summarize the results, the New York Health Insurance Plan's study (and a similar trial, recently reported from Sweden) suggests that about a fourth of the total mortality from breast cancer (that is, a fourth of some 35,000 deaths a year) might be prevented if all women in the U.S. over the age of 50 were offered a free examination every one to three years. The

			DEATHS FROM OTHER CAUSES IN FIRST FIVE YEARS		BREAST CANCERS DETECTED IN FIRST FIVE YEARS		DEATHS FROM BREAST CANCER IN FIRST NINE YEARS	
		NUMBER OF WOMEN IN EACH GROUP	NUMBER	DEATHS PER 1,000 WOMEN	NUMBER	INCIDENCE PER 1,000 WOMEN	NUMBER	DEATHS PER 1,000 WOMEN
TEST GROUP	EXAMINED	20,800	421	20	225	11	63	3.0
	REFUSED	10,200	429	42	74	7	28	2.8
	TOTAL	31,000	850	27	299	10	91	2.9
CONTROL GROUP	TOTAL	31,000	877	28	285	9	128	4.1

SCREENING FOR EARLY DIAGNOSIS of breast cancer can sometimes intercept the disease before it has spread, as a study funded by the National Cancer Institute indicates. The study followed 62,000 women between the ages of 40 and 64 who were covered by the Health Insurance Plan of Greater New York. The women were divided randomly into two groups: a test group and a control group. Those in the test group were offered a free annual check by physical examination and X-ray mammography for early evidence of breast cancer. About two-thirds of the women in that group chose to have at least one examination during a four-year period. Those in the control group were given no special encouragement to be examined and were left undisturbed. After nine years of follow-up the test group suffered significantly fewer deaths from breast cancer (91 deaths) than the control group (128 deaths).

expense of such a program (more than $100 million per year) has stopped it from being widely adopted, but at least the estimates are there, ready to be brought into any calculation of priorities, costs and benefits.

The other main screening procedure currently in use is the Pap smear, or Papanicolaou test, for the early diagnosis of precancerous changes in the cervix. Overall, on a worldwide basis, carcinoma of the cervix is the commonest lethal cancer of women. Like most other forms of cancer, but unlike breast cancer, it is much commoner among the poor and the less-educated than it is among the educated. In the U.S., for instance, the rates in the highest and the lowest social classes differ about fivefold.

The Pap smear was invented in the late 1920's by Aurel Babès in Bucharest and developed by George N. Papanicolaou of the Cornell University Medical College. The test involves the microscopic examination of cells scraped from the surface of the cervix, at the entrance to the uterus. In the years following World War II the Pap smear came into use as a way of detecting the early stages in the development of cervical cancer. By now it has been applied one or more times to at least 75 percent of the adult women in the U.S. No attempt was made to set up a properly controlled trial like the breast-cancer trial, and for this reason the benefits of the test have not been precisely established. Indeed, the issue is complicated.

The mortality from cervical cancer in the U.S. has been steadily declining probably since the 1930's, presumably because during this period the average levels of hygiene, affluence and education have gone up. Since the Pap smear was introduced in the U.S. at a time when cervical cancer was already on the decline, overall national mortality figures cannot be used as evidence for its success. Nor is it fair simply to compare the mortality among women who have been tested with the mortality among those who have not; in the absence of strong pressure the better-educated will be more likely to agree to testing than the less-educated, and so they would be expected to have a lower mortality from cervical cancer even if the test were of no benefit.

The case for the effectiveness of the Pap smear rests on two separate observations. First, whenever it is possible to compare otherwise similar populations of women who were offered testing programs that started at different times (for example, the women in the different provinces of Canada or the different Scandinavian countries), it does seem that the decline in mortality from cervical cancer invariably accelerated at the time testing became widespread. Second, women who are found to be in the early stages of cervical cancer but who do not then return to the clinic for treatment subsequently experience a much higher mortality from cervical cancer than the women who do return for treatment. Neither of these arguments is absolutely ironclad, but together they are strong enough to make it no longer ethical to conduct a proper trial of the Pap smear.

At various times attempts have been made to establish programs for the early diagnosis of other kinds of cancer. Screening programs for cancer of the skin and mouth have proved effective. Unfortunately few of the sites of the common lethal cancers are as accessible as the breast, the cervix, the skin and the mouth, and there is little sign so far that any of the other programs will prove worth applying on a large scale. In principle, screening programs can succeed only for those cancers characterized by an early precancerous state that is detectable or for those cancers that commonly go through a prolonged stage in which they are detectable but still have not spread beyond the reach of surgery.

Regrettably, not all types of cancers fall into either of these categories. Some years ago, for example, a large-scale trial of the early diagnosis of lung cancer indicated that no great benefit comes from having the disease detected by chest X rays before it has produced any symptoms; it seems that by the time most lung cancers are detectable they have spread too far to be treated. For each type of screening program it is therefore important to set up, early on, a proper trial on a randomly selected group of subjects, because there is no intuitive way of knowing which cancers can be intercepted by early diagnosis.

To summarize, screening programs for earlier diagnosis sometimes bring benefits and sometimes do not. Aside from questions of efficacy, however, it seems unlikely that any country—even one as rich as the U.S.—will ever be

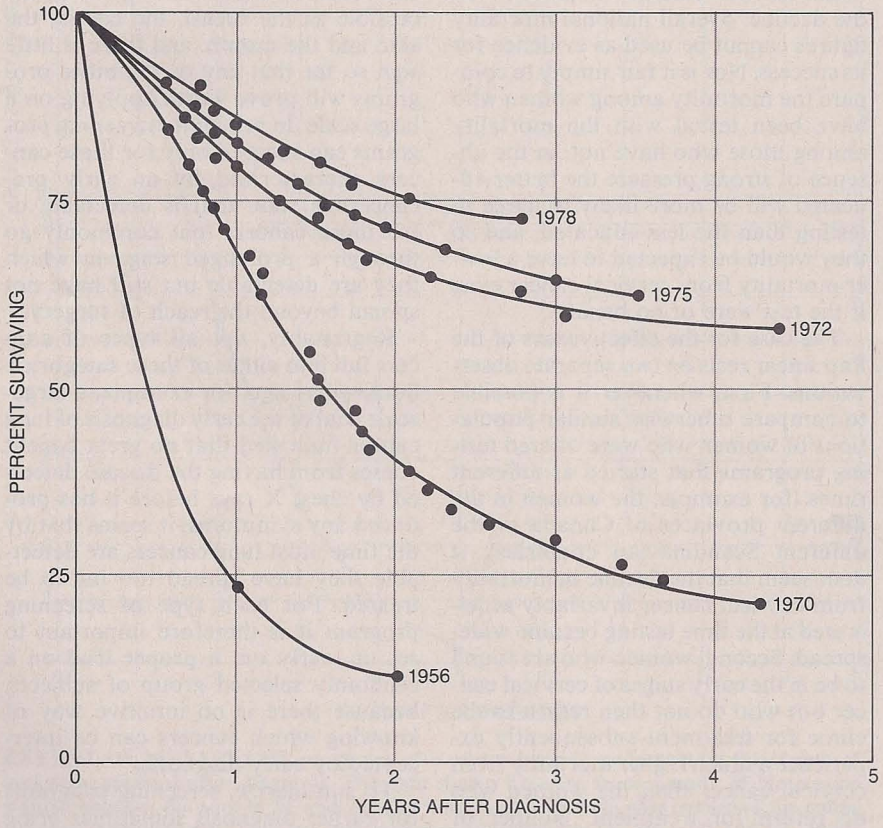
able to afford to test the majority of its population annually for the earliest signs of each of the major cancers.

It remains a depressing truth that fewer than 50 percent of cancer patients can be cured by surgery. A tremendous effort has therefore gone into discovering adjuvant forms of treatment that can be given following surgery. The three widely employed techniques of adjuvant therapy are hormonal treatment, X-irradiation and chemotherapy.

Hormonal treatment is the obvious form of adjuvant therapy to apply to cancers that arise in hormone-responsive tissues such as the breast and the prostate gland. Beginning in the 1890's the ovaries were removed from women who had spreading breast cancer in the hope that the consequent drop in circulating estrogens would slow the growth of the cancer cells. To achieve the same effect without removing the ovaries certain structural analogues of estrogen such as tamoxifen are now employed, which work by blocking the estrogen receptors of the cancer cells. Similarly, the growth of prostate cancer can often be slowed or inhibited by removing the testes or by giving the patient estrogens. Although not all breast and prostate cancers respond to hormonal control, one advantage of this form of adjuvant therapy is that its side effects are usually minor.

Soon after Wilhelm Roentgen discovered X rays in 1895, investigators found that the radiation could damage human tissues. As a result X rays were soon being tested as a means of treating breast cancers that had undergone local recurrence after surgery. X-irradiation is now one of the mainstays in cancer therapy. But there are limits to its use. Excessive whole-body irradiation damages the immune system, the bone marrow and the lining of the intestines. It is the damage to these tissues that is the basis of radiation sickness. (We now interpret most of the effects of radiation in terms of damage to the genetic material, DNA, and this will presumably tend to be greatest in the tissues undergoing the fastest cell division because the more often a cell divides, the less time it has available for the repair of any damage to its DNA.) The treatment of cancer by X rays therefore depends on the relative sensitivity of the cancer compared with the normal tissues that surround it and on whether the radiation can be concentrated on the cancer.

How much radiation can be tolerated by each part of the body is now accurately known. Furthermore, it is feasible, with the high-energy X rays available today, to concentrate radiation into any target organ quite precisely. It has therefore become possible to treat the more sensitive cancers such as Hodgkin's disease, cancer of the cervix and one kind of testicular cancer without producing an unacceptable level of radiation sickness. The majority of cancers, however, cannot be cured by radiation because the dose of X rays required to kill all the cancer cells would also kill the patient.



CHEMOTHERAPY has greatly improved the prospects of survival for children who have leukemia. Only about 10 percent of the children diagnosed in 1956 as having leukemia were still alive two years after diagnosis; by 1978 the number of two-year survivors was roughly 70 percent. The data are from Denman Hammond of the Children's Cancer Study Group.

The next major contribution to the treatment of cancer, cytotoxic chemotherapy, originated with the observation that one of the long-term toxic effects of the mustard gases used in World War I was damage to the bone marrow. (Incidentally, just like X rays, these highly reactive, toxic chemicals proved capable of damaging DNA.) Not long after World War II, when the mutagenicity of mustard gases ceased to count as a military secret, trials were undertaken to test the efficacy of such radiomimetic chemicals (chemicals that produce effects similar to those of radiation) in treating cancer. The early results were encouraging, and in the next 20 years many more chemicals were added to the list of drugs used for chemotherapy.

At present a large number of chemotherapeutic agents are employed, in one combination or another, for the treatment of cancer. Some are prepared synthetically (for example cyclophosphamide, certain nitrosoureas and more recently certain organic metal compounds such as *cis*-platinum). Others are natural toxins (for example plant alkaloids such as vincristine and fungal toxins such as the actinomycins). Nearly all these reagents bind to DNA and cause damage that the cell cannot repair properly. This seems to be the basis of their toxicity, for both the cancer cells and the normal tissues of the body. The other group of chemicals currently in use are certain antimetabolites that block the synthesis of DNA or its precursors (for example fluorouracil, cytosine arabinoside and methotrexate).

The first efforts at chemotherapy concentrated on childhood leukemias and lymphomas for two reasons. First, these cancers, because they are dispersed from the outset, were almost inevitably fatal. Second, the patients, because they were young, had much more to gain from a cure than old people. Although it proved quite easy to achieve a temporary remission with chemotherapy, in nearly every instance the cancer eventually returned,

and it subsequently resisted further chemotherapy. This was not really surprising because even the smallest detectable cancer consists of at least a billion cells; any population of cells as large as that can be expected to contain some variants that are better at growing in the face of selection pressure. As a result two principles have become established that—rightly or wrongly—have determined the subsequent development of most kinds of chemotherapy. If all the cells in a cancer are to be destroyed, it may be necessary not only to use each chemical agent at the highest tolerable level but also to use different agents simultaneously.

With suitable combinations of chemicals it is now possible to cure many kinds of childhood cancer that would otherwise be rapidly fatal. For instance, most children with leukemia can now apparently be cured; to be more precise, a minority relapse and die during or soon after the end of their course of chemotherapy, but the majority enter what at the very least is a prolonged period of relapse-free survival. The hope now is that these survivors will prove to have a normal life expectancy. Similar results have also been recorded for other childhood cancers. The best measure of these successes is to be found in the national mortality statistics. In the early 1950's in the U.S. about 1,900 children under the age of five died of cancer each year. The rate is now down to about 700 per year, suggesting that two-thirds of all children with cancer are now being cured of it.

The reduction in the annual mortality of older children and young adults has been less spectacular, with the following notable exceptions. Hodgkin's disease used to be inevitably fatal, but now most patients can be cured. This represents a saving of some 1,000 lives in the U.S. each year for all age groups combined. About 35 percent of testicular cancers were fatal before chemotherapy, but now roughly a third of these deaths can be prevented, a saving of some 300 lives a year. Finally, choriocarcinoma, a rare cancer of the placenta that occurs about once per 40,000 pregnancies in the U.S., can now be cured by chemotherapy, a saving of perhaps 20 to 30 lives a year. Overall, however, the gains have been limited. The latest figures for the U.S. show about 7,000 deaths per year from cancer under the age of 30, compared with the 10,000 we would have expected if the death rate had remained unchanged since the 1950's.

It is important to note that so far in this discussion there is no discrepancy between the total number of cures estimated from the apparent cure rates for certain cancers and the actual change in the inventory of deaths recorded at the national level. Each year about 3,000 patients under the age of 30 are being cured by chemotherapy who otherwise would have died.

Only 2 percent of the patients who die of cancer are under 30, however. For the vast majority of cancers, which arise in older patients, the results of chemotherapy are much more controversial. The figures on mortality, assembled and published by the statisticians at the National Cancer Institute, show several major changes in the past 25 years. Deaths from lung cancer are on the rise, particularly in women, as the delayed result of the increase in cigarette smoking. Deaths from cervical cancer are going down, thanks in part to the Pap smear. The death rate for stomach cancer continues its unexplained downward trend, which started in the 1930's, and many less common cancers are drifting slightly in one direction or another. Apart from the success with Hodgkin's disease, childhood leukemia and a few other cancers, it is not possible to detect any sudden change in death rates for any of the major cancers that could be credited to chemotherapy. For the old and middle-aged, therefore, the picture is more one of stability than it is one of change.

Those who organize cancer centers and supervise the many clinical trials of chemotherapy look for ways to circumvent these relentless statistics. Sometimes they explain away the unchanging statistics for mortality by pointing out that the national statistics are inevitably a few years behind the times and therefore do not reflect the most recent advances in treatment. Although this point is absolutely correct, it has been made repeatedly in the past 10 years but has never been vindicated by national statistics when these eventually became available. For the most part, however, the organizers disregard the figures for mortality and simply point out that the fraction of patients who are still alive five years after diagnosis has been steadily increasing for nearly every kind of cancer. They attribute this increase in five-year survival to steady improvements in methods of treatment.

Before we conclude that the statistics for mortality are unreliable we should, however, consider whether there could be any systematic error in the national figures for survival rates. As we have seen, it is possible to translate the results of clinical trials into numbers of lives saved on a national scale when considering cancers such as childhood leukemia, where the diagnosis is not in doubt and the outcome depends entirely on whether the treatment is successful or not. But for cancers that are not invariably fatal the calculation is fraught with difficulty because it turns out that we have no certain way of estimating how many lives are waiting to be saved.

To take one rather extreme example, a fourth of all U.S. males over the age of 70 who have died from other causes can be shown on routine postmortem examination to have small cancers of the prostate. We know from incidence data, however, that fewer than 10 percent of those cancers were destined to produce symptoms and still fewer would have proved fatal. Therefore any campaign to detect and treat prostate cancers while they were still small and before they had produced any symptoms is certain to include many "cancers" that would not have been detected except for the campaign. Even if the campaign saved no lives, the inclusion of these additional, nonfatal "cancer" cases would inevitably increase the proportion of "patients" who survived.

Something like this appears to have happened in the U.S. over the past 30 years. Although clinical trials have failed to demonstrate any major advances in the treatment of cancer of the prostate since the introduction of hormone therapy in the 1940's, the five-year relative survival of cases is reported to have gone up from 43 to 63 percent. The national statistics, however, show that it is the reported incidence of new cases that has changed, going from 400 per million men per year in the late 1940's to about 700 per million per year in the late 1970's; the death rate has remained steady at about 210 deaths per million per year. The survival rate has therefore increased not because fewer men are dying from prostate cancer but because more men are being classified as having prostate cancer.

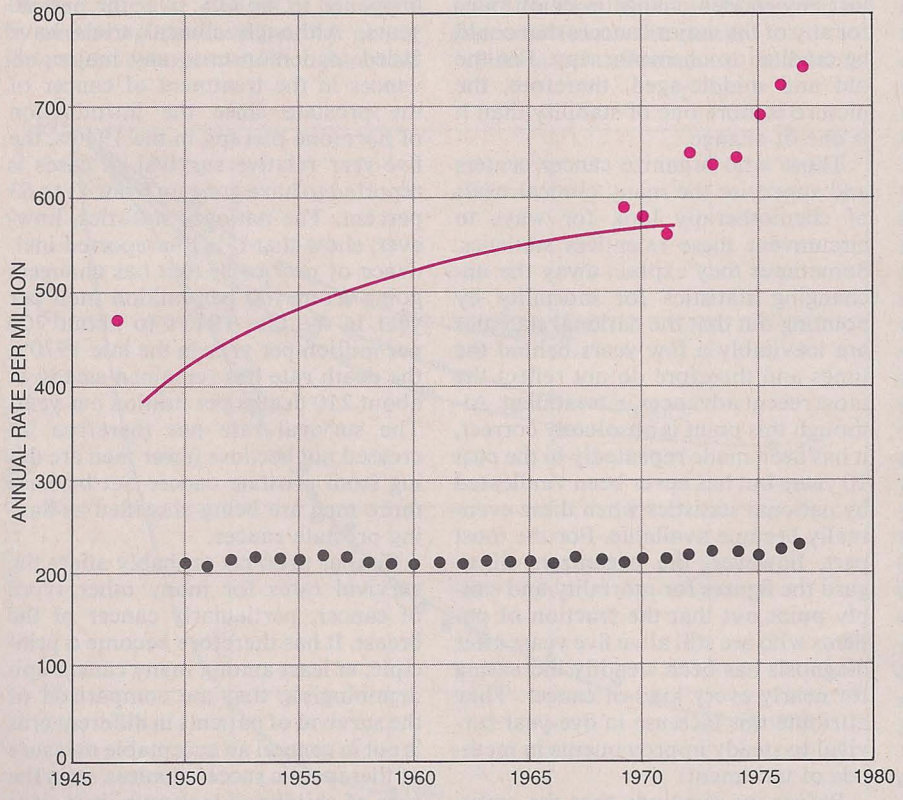
Similar artifacts probably affect the survival rates for many other types of cancer, particularly cancer of the breast. It has therefore become a principle, at least among many cancer epidemiologists, that the comparison of the survival of patients in different eras is not in general an acceptable measure of therapeutic success (unless, as in the case of childhood leukemia, it is clear that there has been no change in the definition of what constitutes disease). For most forms of cancer, therefore, physicians are forced back once again to the "inflexible arithmetic" of clinical trials. Groups of patients must be separated at random and given the various rival treatments. The average survival rates of the subgroups will

then show which treatments do good and which do harm.

The best-studied case concerns the use of various adjuvant therapies following surgery for breast cancer. Recently the results from a large number of trials have been brought together and summarized. Altogether the trials covered about 5,000 women who were treated with various toxic chemotherapeutic agents. A similar number of women, selected at random, received no extra treatment after surgery. The patients have now been followed for between one and 10 years. During this period the treated group as a whole has had about 25 percent fewer deaths than the control group; for women under the age of 50 the reduction has been by about a third. Whether these patients have really been cured by their treatment will not be known until the two groups have been followed for many years, but even if there has been only a postponement of death, this may have been worthwhile. In any event, the chemotherapy of breast cancer can offer real benefits, although so far they are rather modest and not to be compared with the results for certain childhood cancers.

Armed with just these facts, it would be tempting to conclude that chemotherapy should be given to every woman with breast cancer; after all, one-third fewer deaths among women under 55 could conceivably be translated into saving 2,000 or 3,000 lives each year in the U.S. alone. The actual story, unfortunately, is more complicated than these statistics suggest. A six- or 12-month course of chemotherapy not only is a very unpleasant experience but also has its own intrinsic mortality. Furthermore, many of the drugs used are known to be carcinogenic, and one of the long-term effects of chemotherapy is that somewhere between 5 and 10 percent of the surviving patients die of leukemia in the first 10 years after treatment. These may seem like relatively minor hazards for a patient who has an advanced and rapidly growing cancer, but they would be serious considerations for a woman who has a small and apparently localized cancer of the breast. Her chance of dying of her cancer within five years is only about 10 percent even if she receives no additional treatment after surgery.

Still other considerations come into the decision. The same set of trials also included a large study of treatment with the estrogen-inhibitor tamoxifen. This too produced a significant reduction in the number of deaths, although perhaps not as large as the reduction brought about by chemotherapy. (It is interesting that tamoxifen seemed to be most effective in women over 50, whereas cytotoxic chemotherapy seemed to be most effective in younger patients.) Since tamoxifen generally produces only minor side effects, its widespread use could be advocated more readily than the widespread use of cytotoxic drugs. The issue now is to decide whether cytotoxic chemotherapy has anything to offer patients with breast cancer that cannot be achieved with tamoxifen. Judging from the available trials, the likeliest answer is that many young patients can be benefited, but for patients over 50 the combination of chemotherapy and tamoxifen does not seem to produce better results than tamoxifen alone.



INCREASE IN SURVIVAL of cancer patients occurs if the definition of what constitutes a cancer is widened to include conditions that are not destined to be fatal. This appears to be the explanation for the reported increase in survival of men with cancer of the prostate. Between the late 1940's and the late 1970's the mortality rate in the U.S. (*black dots*) has remained steady at about 210 deaths per million men per year. In the same period, however, the number of reported cases has risen from about 400 per million per year to about 700. (The colored dots show the incidence recorded in various national surveys and the colored line shows the increase recorded in Connecticut.) The increase in incidence is presumably the reason the five-year survival of men with cancer of the prostate has increased from 43 to 63 percent over 30 years although trials have not shown any major advance in treatment.

The role of chemotherapy in the treatment of the other major cancers of adults is much less well documented. Various trials have suggested that in adults some cancers such as ovarian cancer do sometimes respond to chemotherapy. In addition chemotherapy and local irradiation can be used to shrink cancers that arise in inaccessible sites such as certain regions of the head and neck. Overall, however, in terms of duration of survival the results have been more often negative than positive. One recent report, for example, described a trial of chemotherapy in the treatment of colon cancer. More than 600 patients who had received standard surgery were randomly allocated to various forms of adjuvant therapy. Roughly half of the patients received cytotoxic chemotherapy (fluorouracil and an alkylating agent), but their survival proved to be indistinguishable from the survival of the controls, who received no additional treatment. Of the roughly 190 patients who had chemotherapy and did not die of their cancer in the six-year trial period, one patient died from the immediate consequences of the treatment and seven died of leukemia.

In spite of these rather sobering findings several cytotoxic drugs are now commonly employed. The Connecticut Cancer Registry, for instance, reports that about a fourth of all cancer patients are recorded as having some

form of chemotherapy during their initial stay in the hospital. The National Cancer Institute estimates that more than 200,000 patients receive chemotherapy in the U.S. each year. For a dangerous and technologically exacting form of treatment these are disturbing figures, particularly since the benefit for most categories of patients has yet to be established. Furthermore, the number of patients who are being cured can hardly amount to more than a few percent of those who are treated.

All told, adjuvant treatments now avert a few thousand (perhaps 2 or 3 percent) of the 400,000 deaths from cancer that occur each year in the U.S. Even without the invention of any additional drugs this figure might conceivably be pushed up to 5 percent; an extra 1 percent, for example, could possibly come from the treatment of breast cancer with cytotoxic agents. These are very real gains and a fitting memorial to the many thousands of patients who took part in the early trials of chemotherapy.

The fortitude and altruism of these patients have not, however, been matched by any comparable sense of responsibility on the part of those who determine national policies. By the 1960's cigarette smoking had been established as the major cause of lung cancer. Since then, however, few nations have made much of an effort to contain the further expansion of the tobacco industry. Unfortunately there are huge financial incentives for nations to sit back and do nothing. The cigarette is a readily taxable commodity; in the U.S. it provides the Federal and the state governments with about $6 billion a year. More important (at least for the British government, and perhaps also in the eyes of the U.S. Government), smoking cuts down the bill for old-age benefits because it reduces life span.

At the price of a slight increase in costs for health care the current smokers in the U.S. will on the average each have saved the U.S. Government about $35,000 in Social Security payments simply because they will on the average die sooner than nonsmokers; most of the deaths occur after retirement and are not from cancer but from cardiovascular disease and chronic lung disease, the incidence of which is also raised by smoking. The loss of life span represents a total saving of some $10 billion a year over the next half century or so.

Some countries have banned all tobacco advertising, and this has had an almost instant effect on tobacco sales. The failure of the U.S. Government to take such a step far outweighs all the advances made in the treatment of cancer since the advent of modern surgery. From 1953 on lung cancer has been the commonest fatal cancer in American males, and about now it is expected to surpass breast cancer and become the commonest fatal cancer in females. The waste of life is truly astonishing. Thanks to the cigarette, the U.S. now suffers a completely unnecessary additional 100,000 deaths per year from lung cancer. These numbers dwarf the 5,000 to 10,000 lives that are being saved by chemotherapy. So far the war against cancer is being lost because (to stay with the metaphor of war) we continue to tolerate the presence of a fifth column in our midst.

The conquest of the commonest of all lethal cancers depends, therefore, on the will power of governments and not on the skill of physicians or the ingenuity of scientists. Fortunately the affluent and better-educated are now smoking less than they used to. Because they tend to set the pace, the trend may eventually spread to the population as a whole.

For the other major cancers the issues are less clear-cut. In order of descending numerical importance these are cancer of the large intestine, breast, prostate and pancreas. Because each cancer is common in some countries and rare in others, each must be driven by external causes that are prevalent in some parts of the world and rare or absent in others. Even within the U.S. it is possible to find certain groups of people for whom the death rate from cancer is only about half the average national rate. Surely this proves that most forms of cancer are preventable.

This is not a very startling conclusion. None of the important causes of death has been primarily controlled by treatment. The death rates from malaria, cholera, typhus, tuberculosis, scurvy, pellagra and the other scourges of the past have dwindled in the U.S. mainly because humankind has learned how to prevent these diseases, not simply because they can be treated. Indeed, even cardiovascular mortality (the commonest of all forms of death in developed countries) has begun to decline in the U.S., suggesting that some change in circumstances or lifestyle is tending to prevent its occurrence. And so there are many grounds for believing that when any major disease is tackled on a national scale, the chief effort should be to prevent its occurrence. To put most of the effort into treatment is to deny all precedent.

Cancers of the cervix and of the liver are usually due to a viral infection, and each should be preventable by immunization. This could save 14,000 lives per year in the U.S. and perhaps as many as 500,000 in the world as a whole. The causes of most of the other important cancers are not yet known well enough for anyone to predict how or when they will be prevented. But eventually they will be, because they do have causes that await discovery.

The prospects for great advances in the treatment of cancer are not as obvious. The available cytotoxic drugs are not particularly discriminating in their action, being toxic for any rapidly dividing cell. Indeed, it is at first sight surprising that chemotherapy should ever be successful. It is important to remember, however, that the cancers most effectively treated by chemotherapy fall into rather special classes. First, there are the cancers that arise in cells left over from the process of embryogenesis (the cancers special to infants), in cells of the germ line (certain testicular and ovarian cancers) and in fetal cells trapped in the mother (choriocarcinoma of the placenta). These cancers have in common the unusual feature that they are cells in an alien environment. It is quite possible that the body has mechanisms for destroying such leftovers, particularly if chemotherapy has somewhat reduced their numbers.

The only other cancer readily curable by chemotherapy is Hodgkin's disease. This is a most unusual cancer because it is made up of a mixture of several types of cell and until recently was actually classified as some form of chronic infection. In short, the extreme peculiarity of the list of cancers known to be cured by cytotoxic drugs suggests that the present forms of chemotherapy may be seldom if ever sufficiently specific to kill every cell in a cancer and yet spare the normal tissues of the patient. Whether any of the common cancers can be cured by chemotherapy has yet to be established.

What then can be said about the long-term prospects? No one knows what new forms of chemotherapy may be invented, or when they will be invented. While such discoveries are awaited, more effort should be directed to certain proved forms of screening and much more effort to prevention. It seems bad cost-accounting for the Federal Government to subsidize chemotherapy of the common cancers of adults and not to subsidize the screening of women for breast cancer. Worse, it is surely an act of folly to pour hundreds of millions of dollars every year into giving a growing number of patients chemotherapy while doing virtually nothing to protect the population from cigarettes.