

Introduction



Spontaneous Remission

The Spectrum of Self-Repair

by

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The rare but spectacular phenomenon of spontaneous remission of cancer persists in the annals of medicine, totally inexplicable but real, a hypothetical straw to clutch in the search for cure. From time to time patients turn up with far advanced cancer, beyond the possibility of cure. They undergo exploratory surgery, the surgeon observes metastases throughout the peritoneal cavity and liver, and the patient is sent home to die, only to turn up again 10 years later free of disease and in good health. There are now several hundred such cases in world scientific literature, and no one doubts the validity of the observations.

But no one has the ghost of an idea how it happens. Some have suggested the sudden mobilization of immunological defense, others propose that an intervening infection by bacteria or viruses has done something to destroy the cancer cells, but no one knows. It is a fascinating mystery, but at the same time a solid basis for hope in the future: If several hundred patients have succeeded in doing this sort of thing, eliminating vast numbers of malignant cells on their own, the possibility that medicine can learn to accomplish the same thing at will is surely within the reach of imagining.

*Lewis Thomas, *The Youngest Science: Notes of a Medicine Watcher* [Viking Press 1983, 205].*

REMISSION: THE SCIENCE OF SELF-REPAIR

A new area of biology is emerging: the study of spontaneous remissions from normally fatal illnesses. Of all the astonishing properties of living systems the two most amazing are their ability to reproduce themselves and the ability to repair themselves in a wide variety of ways. As Lewis Thomas suggests, scientists studying spontaneous remission could uncover the mysteries of how the human body can cure itself, turning those mysteries into mechanisms of healing “at will.”

SPONTANEOUS REMISSION: DEFINITIONS

To begin a task such as the overall mapping of spontaneous remission clearly requires some agreement on both the terms and their definitions, and herein lies the problem: There is little or no agreement. In the early 1900s, for example, a number of authors used the term “spontaneous cure.” Rohdenburg¹ used the term “spontaneous recession” in his classic 1918 paper. Other authors have used spontaneous regression when a tumor disappears and spontaneous remission when a disease disappears. Still others have made a distinction between a slowing down of a disease process and its disappearance.

William Boyd², in his 1966 text *The Spontaneous Regression of Cancer*, defined remission as “a temporary amelioration of a condition, to be followed later by an exacerbation. When a tumor has been growing rapidly and then slows down or appears to halt, we speak of a remission.” He points out that remission and regression should not be confused. “In regression, the tumor disappears and the patient is restored to health.”³ The distinction appears to be one of time.

About the term spontaneous he wrote, “It has a suggestion of something happening without a cause. That, of course, is also absurd, for everything has a cause, apparent or inapparent. On consulting the dictionary we find spontaneous defined as ‘without external cause.’ If we add the adjective ‘adequate,’ we have a concept which we can use in our thinking.”⁴ It is important to note that Boyd included prolonged arrest and delayed metastases or delayed recurrence in his definition of spontaneous regression.

Tilden Everson and Warren Cole⁵, whose review of cases from the world’s medical literature and from personal communications was, until now, the only exhaustive analysis of spontaneous regression available,

established the definition of spontaneous regression that, with few additions, has remained the one in most common usage today:

We define spontaneous regression of cancer as the partial or complete disappearance of a malignant tumor in the absence of all treatment or in the presence of therapy which is considered inadequate to exert a significant influence on neoplastic disease. It is not implied that spontaneous regression need progress to complete disappearance of tumor nor that spontaneous regression is synonymous with cure; indeed, we would consider cases in which a tumor underwent apparent spontaneous regression in one area but flourished unchecked in other areas or reappeared at a later date as valid examples of this phenomenon.⁶

In 1975, Yujiro Ikemi, Shunji Nakagawa, Tetsuya Nakagawa and Mineyasu Sugita⁷ analyzed 7 cases of spontaneous remission from cancer “from the psychosomatic point of view.” In their paper they suggested that “Definitions of SRC [spontaneous regression of cancer] vary depending on investigators or the purpose of the particular study being conducted.” They defined the term as follows:

1. The reduction or disappearance of a pathohistologically confirmed tumor in the absence of any active anti-cancer therapy.
2. The long survival of the host body due to extremely delayed progress or prolonged arrest of cancer with no rapid growth or metastases of a malignant tumor.
3. The long survival of the host body with no cachectic change of cancer in the presence of some anti-cancer therapy, or the death of the host body after long survival due to some cause other than cancer.⁸

In search for an appropriate definition for the phenomenon we’ll look [*Webster’s New Twentieth Century Dictionary of the English Language, 1983*] at the original meanings of the words:

- spontaneous [from the Latin *sponte*, of free will] 1. acting in accordance with or resulting from temperament, or disposition, or from a native internal proneness, readiness, or tendency, without compulsion, constraint or premeditation. 2. acting by its own impulse, energy, or natural law, without external cause or influence.
- remission [from the Latin *remittere*, to send back, remit] 1. the act of remitting (in various senses); a natural feeling, releasing, resigning, relinquishing, surrendering, etc. 2. forgiveness; pardon, as of sins or crimes. 3. cancellation of or release from a debt. 4. a lessening; abating; diminution. 5. a temporary lessening of a disease or pain. 6. a lessening of tension; relaxation [Obsolete]. 7. the act of sending back. [Rare]
- regression [from the Latin *regressus*, pp. of *regredi*, to go back, to return] 1. a regressing; a going back; return; movement backward. 2. retrogression. 3. in biology, reversion to an earlier or simpler form, or to a general or common type. 4. in psychoanalysis, reversion to earlier behavior patterns, as to escape from an unpleasant situation.

The original meaning of the word “spontaneous” has little to do with the sense of suddenness, rapidity or immediate change that more contemporary uses of the word imply. Remissions are indeed not usually sudden—they happen gradually over time. The word originally had more to do with the “native internal proneness” of a system, possibly the manifestation of natural inner mechanisms of systems. This casts a different light on the phenomenon. The original meaning of the word remission seems closer to contemporary usage, though it is interesting to note the inclusion of meanings such as forgiveness, and a lessening of tension or relaxation in the dictionary definition. The meaning of regression, as a going back or as a reversion to a general or common type, does seem to have a relationship to tumor regression.

With this history in mind, for this Bibliography we shall use the following definition and, since the authors we will be discussing use both spontaneous regression or spontaneous remission, we shall use the terms interchangeably when we discuss the phenomenon: We’ll define spontaneous remission as “*the disappearance, complete or incomplete, of a disease or cancer without medical treatment or treatment that is considered inadequate to produce the resulting disappearance of disease symptoms or tumor.*”

REDEFINING REMISSION

It is clear that “remission” needs to be reclassified. As we saw, the historical distinction between remission and regression, while interesting, is confusing and unnecessary. Not only is there no standardization of definition, there are no criteria regarding duration of disease free interval necessary to qualify for remission. As a start at redefining remission, we propose first that a new set of criteria be adopted to more clearly reflect different kinds of remissions.

1. *Pure Remission: Remission with No Allopathic Treatment [PR]*

These would be cases where a patient was medically diagnosed, via X-rays, biopsy or other medical tests, who either refused any medical treatment or for whom medical treatment was deemed useless or unavailable who nonetheless recovered. An example of “pure remission” would be a patient diagnosed with bone cancer, who refused medical treatment and is disease-free ten years later.

2. *Treatment-Related Remission: Remission with Inadequate Medical Treatment [TR]*

This is the class where medical diagnosis is then followed for a period of time by one or more kinds of medical treatment, treatment usually known to be insufficient to produce either a cure or a remission and remission occurs.

3. *“Alternative” or Complex Remission [AR]*

More complex cases may also exist where patients have resorted to a complex of traditional medical and so-called alternative treatments. A recent survey of this group suggests that as many as 10% of them undergo “spontaneous” remissions, though the causes for these are so far unstudied.

4. *“Miraculous” Remission [MR]*

Finally, there is the most unusual kind of all—those associated with spiritual cures, such as those carefully documented by the International Medical Commission at Lourdes in France. These cures are sudden, complete and without medical treatment. These cases appear to involve some of the same pathways as remission but consideration should be given to the possibility that the altered states of prayer, religious faith, and meditation may allow the process of self-repair greater freedom to operate.

This preliminary break-down suggests that a complex of conditions need to be considered if a properly designed, systematic study of the subject is to be done. We suggest that along with more adequate definitions criteria regarding the appropriate duration of disease-free interval necessary to qualify for remission must be determined, perhaps established based upon the known epidemiology of the disease progression.

SPONTANEOUS REMISSION—AN ANNOTATED BIBLIOGRAPHY: AN OVERVIEW

While agreeing that the phenomenon of remission is relatively rare, the data from our searches suggest that it may not be as rare as previously believed—certainly more than the several hundred Lewis Thomas mentions. It would appear that the impression of rarity is at least partly an artifact of under-reporting, but our research shows there has been an increase in the number of cases reported in the last twenty years.

Reviews of spontaneous remission have been rare, however, and until now only two texts and one monograph have been devoted to the subject. Both texts appeared in 1966: Tilden Everson and Warren Cole’s text *Spontaneous Regression of Cancer* and William Boyd’s *The Spontaneous Regression of Cancer*, both of which have been out of print for many years. The monograph is the proceedings from the only international conference held on the subject, at Johns Hopkins Medical School in 1974, published by the National Cancer Institute in 1976, and it too is out of print.

Since there is no standard reference for the field, the first task of The Remission Project of the Institute of Noetic Sciences was to search the world’s medical literature. As a result, it assembled the largest database of medically reported cases of spontaneous remission in the world, with more than 3,500 references, from more than 800 journals in 20 different languages. The references collected prior to 1966 (approximately 31% of the references in The Remission Project’s database) had to be collected at medical libraries by a process of “working backwards” since references available from on-line databases only go back as far as 1967. (Cancer references comprise approximately 74% of the collection.)

The Remission Project is now publishing this annotated (including abstracts and case-histories) bibliography selected from the world literature on the subject. The Bibliography shows that spontaneous remission is:

- widely documented in the world medical literature since the end of the last century.
- a phenomenon that occurs across a broad spectrum of diseases and is not limited to cancer, though cancer does make up the bulk of the reports.
- potentially an extremely rich area of research that can allow us to see important, little-known biological and psychological processes in a way that may provide important clues to understanding the self-regulating processes in the body.

If the phenomenon of spontaneous remission is indeed widely documented, and the study of it holds such potential for our understanding of health and healing, why is it that there is no ongoing, up-to-date review of the literature? The primary need in organizing a new field is the creation of an overview of available information; this normally progresses naturally throughout the history of medical research as various researchers periodically review the current state of knowledge in any given field. Remission research is an exception: Little systematic attention has been paid to the concept.

There are several possible explanations for this lack:

- Remission is often regarded as an artifact created by the misdiagnosis of the patient's condition.
- Remission does not lend itself to research since it is usually seen after the fact, presumably leaving no traces of how it occurred.
- Clinicians have shown an unwillingness to report their cases in the medical literature, possibly because of fear of criticism from their peers.
- The quality of reports of remission varies widely, making the actual occurrence of spontaneous remission very difficult to estimate.
- Cases reported in the predominantly psychological community report little physical documentation about the patient, and those in the medical/clinical community say little about the patient's personal history.

Some in the medical community suggest that rather than thinking in terms of remission as a distinct state, one should instead think in terms of "time to recurrence." In this view, all remissions are but a temporary respite from the inevitable recurrence of whatever the disease in question may be. However, it seems premature to argue this point at this stage, since the natural history of the phenomenon is unknown. And until it is known, we simply cannot determine whether there are classes of remissions that are "complete" and others which are more properly regarded as temporary abatement until recurrence.

Spontaneous Remission—An Annotated Bibliography is organized according to the *International Classification of Diseases [ICD•9•CM]*⁹ system. It is divided into three sections: "Part One: Remission of Cancer" with ten chapters, "Part Two: Remission of Diseases Other Than Cancer" with nine chapters, and "Part Three" which contains four Appendices and an Addendum. Each section contains annotated bibliographic citations (including summaries and in some cases complete text of case reports) and supplemental references.

The cases reported in the main body of the work have been selected as most representative of those cases in which there was little or no allopathic intervention or where, according to the attending physicians, the treatment received was considered inadequate to produce the resulting remission. Also included in each chapter are supplemental references for the reader who wishes to pursue in depth a particular disease or type of cancer.

The four chapters in the appendices provide a historical perspective on remission, with chapters containing review articles, behavioral and spiritual reports of remission, clinical and experimental studies, and an extensive analysis of the cases where remission was associated with infection or fever whether naturally occurring or induced by toxin therapy.

SPONTANEOUS REMISSION—AN ANNOTATED BIBLIOGRAPHY:

SUMMARY OF ARTICLES AND CASE REPORTS

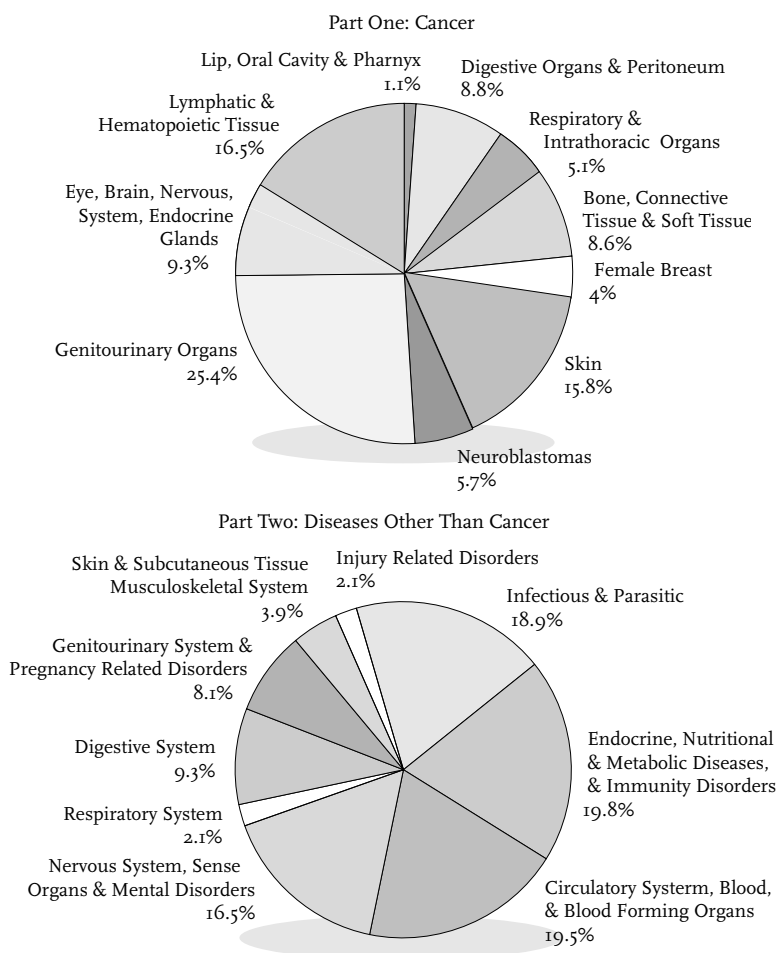
There are 1385 different articles cited in the bibliography: 1051 are references to the spontaneous remission of cancer, 334 to diseases other than cancer. Of the 1051 cancer references, 426 or almost 41% were published prior to 1966, of the references to diseases other than cancer, 38 or 11% were published before 1966.

Some articles appear in more than one chapter because they refer to more than one type of cancer or disease other than cancer. When duplications are considered there are a total of 1574 citations.

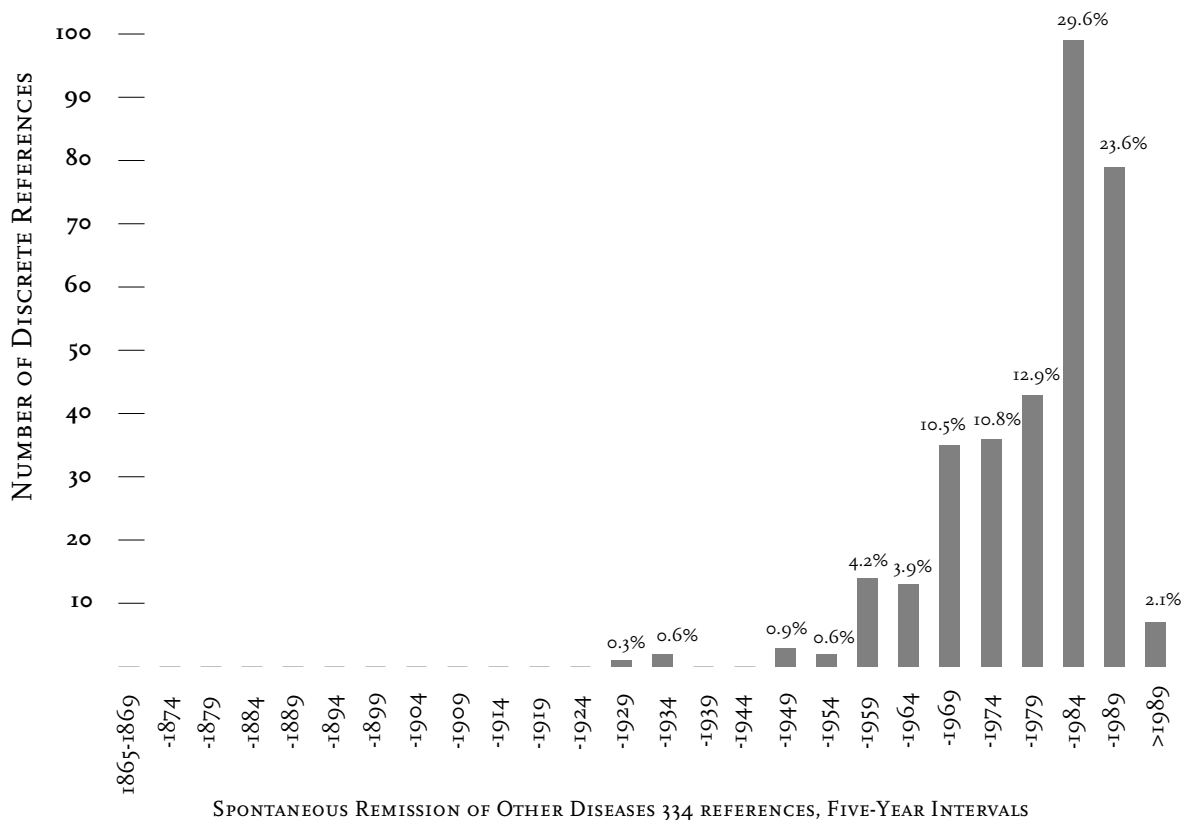
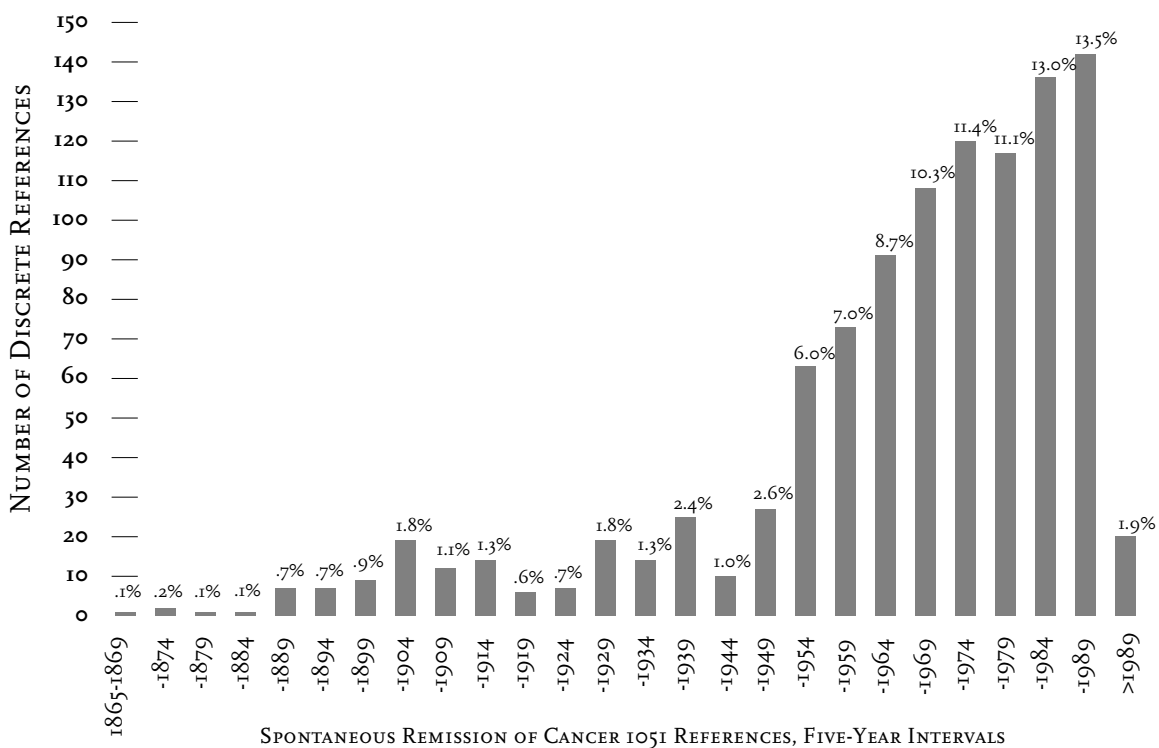
	Total Citations †	Annotated	Supplemental	Case Reports
Neoplasms	874	298	576	261
malignant	755	241	514	216
benign	93	48	45	29
uncertain	26	9	17	16
Other diseases	334	185	149	120
Appendices	366	236	130	51††
Totals	1574	719	855	432

† with duplications considered
 †† cases not reported in any other sections

The distribution of references in Parts One and Two is displayed in graphic form. Genitourinary neoplasms make up the largest number of references in Part One and infectious and parasitic diseases the largest number of references in Part Two.



Two bar graphs are presented that plot the number of discrete references (with duplications removed from the analysis) as a function of time (five-year intervals). The graphs are presented separately for references to cancer and to other diseases. Reports of spontaneous remission of cancer comprise approximately 70% of the references in the Bibliography.



The progress of a cancer is normally accompanied by regressive or curative processes. The recorded cases of natural repair of cancer, far from being anomalous and exceptional, merely illustrate more strikingly than usual the natural laws which govern every case of the disease. The order of Nature admits of no real anomalies, and is often best brought to light by the close study of apparent exceptions.

1909: W. S. Handley, "The Natural Cure of Cancer," *British Medical Journal*, 582-589.

REMISSION: AN EPIDEMIOLOGICAL UNKNOWN

We are at the threshold of a new field of inquiry. There is no known epidemiology of remission, since the distribution of the phenomenon has never been mapped, although there is a full epidemiology of cancer's incidence, survival and mortality. Since remission happens with unknown frequency it can convincingly be argued that some of both conventional and unconventional therapies' "successes" are simply cases of remission and have nothing to do with the efficacy of either conventional or unconventional therapies.

A major part of the modern battle against cancer has been the detailed tracking of the disease epidemiologically, keeping statistics on which kinds of cancer are found where in the country and who gets them in terms of race, sex, age and other major categories. This effort is organized in the United States by the National Cancer Institute which operates the National Tumor Registry, a clearinghouse for cancer data reported by participating states' tumor registries. Through this effort it is determined whether cancer is increasing or declining; it is also the only way of monitoring the effectiveness of the various treatments. The SEER Program [Surveillance, Epidemiology and End Results] of the National Cancer Institute, established in 1972, monitors the incidence of cancer, and survival and mortality of patients.

There have been many efforts to determine whether or not patients with cancer are living longer today than they did in previous years. The National Cancer Institute argues that they are. Various critics ranging from the General Accounting Office (GAO) of the United States Government to Dr. John Cairns at Harvard argue that the opposite is true. A report from the GAO entitled *Cancer Patient Survival—What Progress Has Been Made?* from March 1987 stated:

Advances in the detection and treatment of cancer from 1950 to 1982 have extended patient survival in all but 1 of 12 cancers GAO examined. GAO concludes, therefore, that progress has been made. However, the extent of improvement in survival for specific cancers is often not as great as that reported. One reason is that biases artificially inflate the amount of 'true' progress.

GAO has also determined that the improvements in patient survival have been most dramatic for the rarer forms of cancer and least dramatic for the more prevalent cancers. As a result, even though the absolute number of lives extended is considerable, this number remains small relative to all cancer patients.¹⁰

Drs. Cairns¹¹ and Bailer¹² have argued that manipulation of the statistics has been the principal reason why it appears that patients are surviving longer. They contend that chemotherapy is not the great success story it is painted to be by its advocates. According to Drs. Bailer and Smith, ". . . we are losing the war against cancer, notwithstanding progress against several uncommon forms of the disease, improvements in palliation, and extension of the productive years of life. A shift in research emphasis, from research on treatment to research on prevention, seems necessary if substantial progress against cancer is to be forthcoming."¹³

MAKING THE UNKNOWN KNOWN: A NATIONAL REMISSION REGISTRY?

Regardless of the arguments about the accuracy of the statistics, the epidemiology of cancer incidence, survival and mortality is available. One way to determine an overall epidemiology of remission would be to establish a National Remission Registry modeled after the National Tumor Registry. In that way, information on spontaneous remission could be collected and cases of remission tracked in a systematic manner. It is generally accepted that spontaneous remission is a natural phenomenon whose causes remain unknown at the present.

With a National Remission Registry to collect data, questions such as the following could begin to be addressed:

- In which diseases is remission most common?
- What is the duration of remission and does that vary with disease type?
- What is the distribution of remission in the United States and world-wide?
- In which people, with which kinds of backgrounds, socially, psychologically and environmentally, does remission occur?
- Are there particular psychological, social or other settings such as habits, lifestyle changes, support groups that act as significant biological response modifiers to trigger remission?
- Are there genetic factors that predispose certain people toward remission?
- Are the factors involved biological or psychobiological or both?
- Is remission mediated by neural or immune mechanisms or both?
- Are there spiritual or attitudinal correlates of remission?

Only when we begin to address these most basic questions can we start to determine the epidemiology of remission. The building of such an epidemiology could lead to increased understanding of disease and treatment and the ability to advise patients more precisely regarding prevention and outcome.

REMISSION: AN EMERGING PHENOMENON IN MEDICINE

Now, through computerized searching techniques, one can conduct medical and scientific literature data-searches on reports of remission from 1966 onwards (only literature from that date on is contained in the medical databases).

An overview of what one now encounters on the subject in the medical database “Medline” is shown by the following chart:

SUMMARY OF MEDLINE SEARCH DATA ON SPONTANEOUS REGRESSION/REMISSION*

Term Appears	1966-1992	1966-1974	1975-1984	1985-1992
as DESCRIPTOR				
Regression	1,556	583	603	370
Remission	9,047	2,112	5,907	1,028
Total	10,603	2,695	6,510	1,398
as TITLE				
Regression	491	96	192	203
Remission	227	40	85	106
Total	718	132	277	309

*The data above are organized as follows:

Number of references where “spontaneous remission” or “spontaneous regression” are mentioned as a DESCRIPTOR (key subject) in the reference.

A DESCRIPTOR is a key subject of the reference.

Number of references where “spontaneous remission” or “spontaneous regression” occur in the TITLE of the reference.

We see that between 1966 and October 1992, in the Medline database there have been 10,603 appearances of the terms “spontaneous remission” or “spontaneous regression” as a descriptor and 718 appearances in titles. Of these 718 papers, more than 80% of them have appeared in the period between 1975 and 1992 and over 40% appeared in the period between 1985 and October of 1992.

REMISSION OF CANCER: CASE REPORTS

Criteria for inclusion of cases varies widely among the published reviews and across the different types of cancer. Rohdenburg divided his cases into three groups based upon the quality of the diagnostic information. William Boyd accepted cases of long survival with evidence of malignant disease, delayed progression or prolonged arrest, and cases where multiple procedures were used. Everson and Cole required rigorous diagnostic proof of malignancy and accepted cases where a wide range of treatment procedures were used (the key phrase in their definition, which has become the definition to date, is “therapy considered inadequate to produce the regression”). They also, to their credit, followed up as many cases as they could and reported the length of survival of cases contained in their text.

We adopted Drs. Everson and Cole’s definition as the standard for inclusion, including, in some cases, prolonged arrest, or delayed progression. Although long survival of the host body with treatment is an indication that some important psychobiological mechanisms may be in effect and should be studied, in this volume those reports are primarily referenced in the supplemental references sections.

DISTRIBUTION OF MALIGNANT CASES REPORTED (N = 216) IN FIVE-YEAR PERIODS

An analysis of the cases of remission of malignant neoplasms over time reported reveals that approximately half of the cases included in this volume were reported in the world’s medical literature after Everson and Cole’s review was published in 1966.

Five-Year Period	Cases	Five-Year Period	Cases
before 1865	1	1930-1934	2
1865-1869	0	1935-1939	5
1870-1874	0	1940-1944	1
1875-1879	0	1945-1949	6
1880-1884	0	1950-1954	14
1885-1889	3	1955-1959	17
1890-1894	1	1960-1964	32
1895-1899	2	1965-1969	13
1900-1904	2	1970-1974	21
1905-1909	3	1975-1979	23
1910-1914	4	1980-1984	24
1915-1919	3	1985-1989	28
1920-1924	0	1989-1990	3
1925-1929	8		

SUMMARY OF CASE REPORTS OF SPONTANEOUS REMISSION OF CANCER CITED BY O’REGAN AND HIRSHBERG (N = 261)†

The following chart is a complete listing of all the cases of spontaneous remission of cancer reported in Part One of this volume.

†This figure includes benign neoplasms (N = 35) and neoplasms of uncertain behavior (N = 10).

Tumor Type/Site	Cases	Possible Explanations for Remission (as reported in article)
Oral cavity & digestive organs	25	
esophagus	1	esophageal bypass
stomach	6	fever, pregnancy, gastrectomy, hepatitis, laparotomy, biopsy, abscess, gastroenterostomy, infection
colon & rectum	6	biopsy, palliative resection, colostomy, wound infection, meditation
liver	4	biopsy, pneumonia, Chinese herbs, blood transfusion
pancreas	3	psychospiritual, biopsy, shock
gall bladder	1	cholecystogastrostomy
parotid gland	1	(adenocystic carcinoma)-diet, palliative radiation
mouth	1	mouth wash
tongue	1	mouth wash
nasopharynx	1	psychospiritual
Neuroblastoma	30	vitamin B12, differentiation, Coley's toxins, biopsy, necrosis, incomplete removal
Breast	22	psychospiritual, meditation, hypnosis, wound infection, resection of primary, erysipelas, arsenicum, ascites (3), cautery, pregnancy, cachexia, typhoid, pleural effusion, Coley's toxins, hypnosis, menopause, diet
Genitourinary organs	58	
chorioepithelioma	3	blood transfusion, hysterectomy, estrogen
uterus	2	diet, laparotomy and biopsy
cervix	3	viola quercitrin infusion, analgesics, biopsy, insulin coma
ovary	3	necrosis, biopsy, fever, analgesics, laparotomy, ascites
testis	2	psychospiritual, orchiectomy
penis	1	biopsy
bladder	2	pulmonary infarction
kidney	42	nephrectomy, plasma transfusion, necrosis, removal of blood supply, radiation, infection, wound infection, biopsy
Bone, connective, & soft tissue	13	
bone sarcomas	6	erysipelas, biopsy, resection, diet, Coley's toxins, psychospiritual (meditation), alternative therapies
soft tissue sarcomas	7	Coley's toxins, biopsy, fever
Skin	21	
squamous cell & epitheliomas	5	erysipelas, infection, biopsy, anti-syphilis treatment, excision
malignant melanoma	14*	incomplete operation, erysipelas, wound infection, regression following pregnancy, laparotomy, palliative radiation, biopsy, hemorrhage, excision, pleural effusion, grape diet, photocoagulation
Kaposi's sarcoma	2	biopsy, removal of immunosuppression
Lungs & bronchii	8	pneumonectomy, change of occupation, fever, nutritional supplements, palliative radiation, biopsy, herpes zoster, meditation, smoking cessation
Lymphatic & hematopoietic	30	
leukemia	17	eclampsia, infection, pleural effusion, pneumonia, analgesics, bacterial infection, sepsis
lymphoma	13	biopsy, measles, laparotomy, resection, bacterial infection
Eye, brain, & nervous system	9	
retinoblastoma	7	fever, enucleation of one eye
brain	2	biopsy, infection
Total malignant neoplasms	216	

* This figure includes 3 cases of melanoma of the eye.

Tumor Type/Site	Cases	Possible Explanations for Remission (as reported in article)
Benign neoplasms	35	
gastric polyps	4	necrosis
polyps of the colon	2	
liver adenoma	2	cessation of oral contraceptives
mesenchymal hamartoma	1	calcification
pulmonary leiomyoma	1	pregnancy and postpartum
cardiac tumors	3	biopsy
osteoblastoma	2	biopsy
osteochondroma	4	x-rays
fibromatosis	6	biopsy, gastrectomy
desmoid tumors	3	menstruation, chinese herbs, biopsy
hemangiomas	4	involution, biopsy
atypical Hurthle cell adenoma	1	biopsy
cystic hygromas	1	
lymphangioma	1	
Neoplasms of uncertain behavior	10	
hemangioendothelioma	3	differentiation, biopsy
Bowen's disease (vulva)	1	biopsy, pregnancy
hydatidiform mole	3	fever, menstruation, after pregnancy
neurofibromatosis	2	
phaeochromocytoma (adrenal gland)	1	pregnancy
Total benign and neoplasms of uncertain behavior	45	

REMISSION OF DISEASES OTHER THAN CANCER: CASE REPORTS

Spontaneous Remission—An Annotated Bibliography is the first survey to report specifically on the phenomenon of remission across the entire spectrum of diseases. Until now, reviews of remission have been dedicated to the analysis of cases of cancer only.

Case reports of diseases other than cancer show a different distribution than cancer. The five-year distribution reflects that difference. Because of the wide range of diseases covered in this section, it is likely that these figures underestimate the true number of cases of spontaneous remission which have occurred over time. The references in this area were collected primarily by conducting on-line database searches. An exhaustive literature search would be necessary to obtain an accurate picture of the scope of the phenomenon of spontaneous remission of diseases other than cancer.

DISTRIBUTION OF CASE REPORTS OF OTHER DISEASES (N = 120) IN FIVE-YEAR PERIODS
Of the 334 references in the bibliography to diseases other than cancer, approximately 38 (11%) were published before 1966. Of the 120 cases reported, 14 (12%) were published prior to 1966 and 106 (88%) after 1966. The following chart reflects the distribution of cases in five-year intervals reported in this volume.

Five-Year Period	Cases	Five-Year Period	Cases
1945-1949	1	1970-1974	8
1950-1954	0	1975-1979	16
1955-1959	10	1980-1984	44
1960-1964	1	1985-1989	26
1965-1969	11	1989-1990	3

SUMMARY OF CASE REPORTS OF SPONTANEOUS REMISSION OF DISEASES OTHER THAN
CANCER (N = 120) CITED BY O'REGAN AND HIRSHBERG

The following chart is a summary of the cases arranged by disease type reported in this volume.

Disease Type	Cases	Disease Type	Cases
Infectious and parasitic diseases	30	Circulatory system disorders	20
HIV	12	Hypertensive disease	1
HIV-serology	3	Ischemic heart disease	2
HIV-Kaposi's sarcoma	2	Arteriovenous malforma-	4
HIV-associated infections	7	Aneurysms	3
Mycoses	7	Diseases of arteries, arteri-	1
sporotrichosis	2	oles &	
other mycoses	5	Budd-Chiari syndrome	1
Molluscum contagiosum	2	Congenital anomalies	8
Warts	7	atrial septal defect	3
Other infectious diseases	2	ventricular septal defect	2
		coronary artery fistula	2
		pulmonary artery anomalies	1
Endocrine, nutritional & metabolic diseases	22	Blood & blood forming organs	2
Hashimoto's thyroiditis	2	anemias	1
Diabetes mellitus	2	coagulation defects	1
Zollinger-Ellison syndrome	1		
Cushing's disease	2	Digestive system diseases	13
Macrocryoglobulinemia	1	Diseases of the oral cavity	2
Histiocytosis	11	Menetrier's disease	2
Amyloidosis	1	Ulcers	1
Disorders of humoral immunity	2	Gallbladder & biliary tract	4
		Pancreatic disorders	4
Nervous system & mental disorders	12		
Central & peripheral nervous sys-	1	Genitourinary system diseases	7
Eye & adnexa	10	Nephritis & nephrosis	1
Congenital anomalies	1	Other urinary disorders	4
		Female genital tract disor-	2
Respiratory system diseases	5		
Asthma	3	Musculoskeletal system diseases	2
Other lung diseases	2	Arthritis	2
Skin & subcutaneous tissue diseases	2	Injury related disorders	5

Questions will surely be raised about some of the reports where spontaneous remission has been associated with practices such as meditation and hypnosis since these cases point out a strong role for the mind in remission. Other reports indicating the remission occurred following transfusion of blood from patients in remission to others with the same disease raise exciting questions about physical blood-borne factors that may one day be isolated and cloned to induce remission. In the present survey there are only indirect hints about the kinds of people to whom spontaneous remission happens and it would seem urgent to begin research on what people in remission have to tell us about their healing process. Perhaps this document will be a first step toward tapping the further research needed.

Cases of spontaneous remission where infections and fever occurred or where Coley's toxins were used to induce fever indicate that the possible stimulation of the immune response may have beneficial effects upon the course of neoplasms.

If human beings possess usually untapped powers of self-repair that can affect the dissolution of a tumor, the regeneration of various organ systems, or the healing of various normally terminal conditions, then it is of vital importance to medicine that such systems be investigated and understood.

SPONTANEOUS REMISSION: HISTORY IN THE MEDICAL LITERATURE

A review of the remission literature reveals that almost all, if not all, the papers written on remission have been about cancer. There have been literally no comprehensive reviews of spontaneous remission of diseases other than cancer. While reports on the epidemiology of diseases like diabetes, heart disease, and certain congenital anomalies have been published, there is no comprehensive look at remissions that occur across a wide spectrum of ailments. This is understandable, since, on the surface at least, it would appear that the mechanisms of remission in heart disease, for example, are very different from those of diabetes, or asthma or the natural repair of a congenital heart defect.

On the other hand, it is assumed that the mechanisms of remission for neoplasms that occur in different organs are likely to be similar and therefore more studyable. Lewis Thomas wrote, "In the end, when all the basic facts are in, I think it will turn out that all forms of cancer, in whatever organs and of whatever cell types, are a single disease, caused by a single, central controlling mechanism gone wrong."¹⁴ So, a review of the history of remission is a review of the history of spontaneous remission of cancer. Most of the information on spontaneous remission of cancer comes from single case reports. Reviews, speculations, and position papers have appeared in the medical literature for at least the last 80-90 years, in other words, as long as there has been histological diagnosis of cancer.

- One of the earliest reviews of remission of malignant growths was collected by Lomer in 1903.¹⁵ He reviewed 213 cases of remission of uterine cancer that occurred chiefly after cauterization.
- In 1906, Gaylord and Clowes¹⁶, in a detailed report on their work with spontaneous cure of cancer in experimentally inoculated mice, found that approximately 23% of the animals experienced a spontaneous cure. Their observations with animals encouraged them to look for spontaneous cure of cancer in humans: "The frequency of the occurrence and its distribution in animals suggests that it may be more frequent in human beings than is generally supposed." After eliminating all those cases in the literature with questionable diagnostic information in the reports, they found 14 cases which were "authentic cases of spontaneous recovery. They include 2 epitheliomata, 1 scirrhous cancer of the breast, 1 malignant adenoma of the rectum, 7 cases of chorion carcinoma, 1 endothelioma, and 2 sarcomas."¹⁷

They found that the regressive changes observed at the margins of the tumors were the same in animals and humans. They also found that once the mice had recovered from the tumor, they appeared to have a resistance to reinoculation they did not have before, and speculated that an immune response had been initiated that precluded development of another tumor.

In conclusion they stated that "the occurrence of spontaneous recoveries from cancer, indicating the existence of immune forces capable of terminating the disease, demonstrates that cancer is not necessarily incurable, and should serve as an additional stimulus to research directed toward the discovery of a serum-therapeutic treatment."¹⁸ Thus, Gaylord and Clowes wrote one of the first papers that speculated that "immune forces" could have a role in the spontaneous remission of cancer.

- W. Sampson Handley¹⁹, in an address before the Royal College of Surgeons in 1909, presented evidence supporting his theories on the mode of dissemination of cancer. The natural history of the cancer process is "one of centrifugal growth followed by centrifugal death"²⁰ although this natural process is a local one, not a constitutional one, and may not prevent the dissemination of the disease. In a review of cases in the literature, he remarked that

The literature of cancer therapeutics does not contain the record of a single fact which cannot be paralleled among the histories of untreated cases. How then is the value of any particular method of treatment to be determined? It is futile to bring forward a few isolated cases in

which the shrinkage or disappearance of primary or secondary growths has been observed, for these phenomena, as we have seen, belong to the natural course of the disease. Their occurrence as testimony to the value of a remedy would only be significant when they [are] frequently and immediately followed upon its employment in a number of consecutive cases.²¹

Handley presented microscopic and macroscopic evidence for the continual repair in carcinomas, the centrifugal spread of repair away from the point of origin of the primary growth, and the life cycle of a typical carcinoma. In his discussion of the therapeutic value of treatments for cancer, he remarked that, aside from the curative properties of Coley's toxins, he has not found evidence that any of the treatments employed at that time provided substantial improvement over doing no treatment at all.

He advocated that the best treatment for cancer is to promote the body's own natural ability to counteract the effects of cancer. Since he had observed that fibrosis seems to occur in conjunction with the natural repair of cancer as well as tuberculosis, he suggested that there could be "apparent benefit to cancer patients as a result of change of residence from town to country, or from a sea voyage,"²² and that open-air treatment should be investigated along with surgery where possible, as a treatment that would promote the natural cure of the disease.

- In 1910, a report by McConnell²³ reviewed the literature on animal studies and case histories of remission of malignant growths. In these cases, after an increase in growth, for unknown reason the cancer underwent regressive changes with partial or complete disappearance.

It is not a matter of any doubt that carcinomatous growths have, after operation, undergone distinct regression and have remained quiescent for many years. If this can occur after operations that could have by no means removed all the neoplasm it does not require much logic to assume that similar processes might occur spontaneously.²⁴

He presented evidence of what he calls "bodily resistance" by citing the animal work of Gaylord and Clowes and others. To support his theory of resistance, he summarized 25 cases from the literature including 5 cases of carcinoma of the breast, 4 cases of colorectal cancer, 2 cases of sarcomas, 1 of the jaw and 1 of the clavicle, 11 cases of stomach carcinoma, 1 case of carcinoma of the cheek and 1 endothelioma. Of particular interest is Dr. McConnell's discussion of the reports from C. G. Mackay and Eugene Hodenpyl on the curative properties of ascitic fluid upon the cancer patient.

In both Dr. Mackay's and Dr. Hodenpyl's cases the remission took place after the formation of large collections of fluid within the serous cavities. The tumor masses then begin to degenerate, become necrotic and are cast off or absorbed as the exudate is taken up into the general system. It would seem that after a certain point has been reached that there are formed in the patient substances that exert a distinctly lytic effect upon the tumor cells. Dr. Hodenpyl's experiments in using the ascitic fluid as a therapeutic measure indicate that there is some substance present in this proteid exudate that exerts an active influence upon the growth. The next step therefore would be the obtaining of a supply of a lytic serum that could be used in the treatment of malignant disease....The curative action of the serum in these instances of regression of malignant growths is apparently not of an antitoxic nature so much as it is that of lysis of specific cells.²⁵

- The first major survey of spontaneous remission of cancer was published by G. L. Rohdenburg in 1918. Dr. Rohdenburg analyzed 302 cases where spontaneous regression, either temporary or permanent, occurred. He excluded cases reported prior to 1890 because the "correctness of the diagnosis is open to very grave question. The factor of diagnostic error in this connection was recognized as far back as 1852."²⁶

He divided his reports into three groups: Group I contained the best reports, "those reports which stand the most rigid scrutiny"; Group II contained cases where "slight question may be raised regarding the adequate control of all possible diagnostic errors"; and Group III contained those cases "open to more

or less grave doubt as to the correct diagnosis." Each of the groups was further divided into (a) cases of complete remission and (b) cases of partial remission. Rohdenburg did not present case summaries of all 302 cases. Only cases whose summaries are presented in Rohdenburg's review will be presented in the following table:

SUMMARY OF CASES OF SPONTANEOUS REGRESSION OF CANCER
 REVIEWED BY ROHDENBURG (N = 185) †
 (GROUP I: 103 CASES; GROUP II: 37 CASES; GROUP III: 45 CASES)

Tumor Type/Site	Cases	Possible Causes of Remission
Oral cavity & digestive organs	27	
stomach	8	1 ascitic fluid, 1 laparotomy, 1 fever
colon & rectum	7	1 incomplete operation
gallbladder	2	
mouth	3	1 erysipelas/1 cachexia
tonsil	3	1 erysipelas
lip	3	
liver	1	
Breast	39	1 wound infection, 1 general infection, 2 erysipelas, 1 ascitic fluid, 1 hot air bath, pregnancy
Genitourinary organs	69	
chorioepithelioma	10	2 fever, 1 incomplete operation, 2 pregnancy
uterus	42	18 curettage followed by hysterectomy, 3 cautery & curettage, 1 incomplete operation
cervix	10	1 fever, 1 incomplete operation
ovary	3	1 incomplete operation
vagina	1	
testis	1	erysipelas
bladder	1	
kidney	1	
Sarcomas	35	
head & neck	6	3 erysipelas, 1 pregnancy & abortion
abdomen	3	1 fever
eye	2	
back	1	1 fever
bone	5	1 fever, 1 erysipelas
hands & arm	2	1 inflammation, 1 exposure to sunlight
face	4	1 erysipelas
lymphosarcoma	5	1 Coley's toxins, 1 erysipelas, 1 syphilis treatment
unspecified site	7	3 fever, 3 incomplete operation
Skin	15	
epitheliomas	13	
face	7	3 erysipelas, 1 smallpox infection, 1 incomplete operation
head & neck	3	1 erysipelas
unknown primary	3	
melanoma	2	1 incomplete operation

† The data in this chart is compiled from the paper by G.L. Rohdenburg, "Fluctuations in the growth energy of malignant tumors in man with especial reference to spontaneous recession," Journal of Cancer Research 3 (1918), 193-225.

Cancers of the breast, uterus and appendages, sarcomas and epitheliomas make up over three-quarters of the cases reported. An analysis of this data reveals that the largest number of spontaneous remissions have occurred following incomplete operation, during acute febrile infections and during alterations in the metabolic processes such as cachexia, artificial menopause or during pregnancy.

Rohdenburg speculated on the causes of remission after incomplete operation. He suggested that these cases should be analyzed according to “what has actually been done at the operation”²⁷ and divided incomplete operation into three types:

1. Cases where tumors have partly or completely receded after a laparotomy, where only a portion of the tumor is removed for histological diagnosis. Dr. Rohdenburg remarked that occasionally high temperatures develop after laparotomy which might have a connection to the remission.
2. Cases where complete removal was impossible but a large part of the tumor was removed. It is possible that inflammatory tissue was mistaken for cancer, and, in fact, the tumor was completely removed. Another explanation the author suggested is that the incomplete removal interfered with the blood supply of the remaining tumor and the tumor died from malnutrition.
3. Cases where heat was applied to the tumor, in particular, uterine tumors, where cauterization was used to ease symptoms such as discharge and hemorrhage. Heat (fever) has been known to have an inhibitory effect upon the recurrence of neoplasms.

In several cases in Rohdenburg’s study remission occurred after an acute febrile infection, particularly erysipelas. Other infections, however, have also been reported to promote remission, among them smallpox, pneumonia, malaria and tuberculosis. The absorption by the body of ascites or other malignant effusions has been shown to have an effect on neoplasms. “These cases are best explained by the cytotoxin or cytolytin formation, even though such antibodies have as yet not been demonstrated by experimental means.”

According to Rohdenburg it is clear that remission can occur in “either sex, at any age period, with any type of malignant tumor, and irrespective of the location of the growth. It occurs after a wide variety of conditions, a proof that no particular one is specific, and it is probable that all the conditions noted are preliminary, so to speak, and act by depressing the proliferative energy of the malignant cell until the defensive forces of the body (cytotoxins, cytolytins) are able to accomplish the final destruction.”²⁸

• A period of almost fifty years passed before another major review of cases of spontaneous remission appeared in print. During that time, most of the papers published were either theoretical or mechanistic in nature with few reports containing more than a handful of cases. The perspectives expressed in the papers during that fifty years are worthy of note. In 1933 an excellent paper was published by the physician Joseph DeCourcy²⁹ in which he speculated on the mechanisms of spontaneous remission of cancer. About the existence of spontaneous remission Dr. DeCourcy wrote:

In view of the general conviction in the past that cancer is an incurable disease, there has naturally been an inclination in cases of this kind to assume that the diagnosis was erroneous—a disconcerting reflection which has led the physician observing the case to keep silent about it, or to place a question mark against his report.

There are no accidents in Nature. These apparent exceptions to the rule that every malignant tumor grows on ad infinitum are illustrations of the working of some natural law of which we are still ignorant. I believe it is of the very first importance to give close study to cases of this kind with a view to gaining an insight, if possible, into Nature’s methods of healing and to discover what can be done to make her work easier.³⁰

The author presented his views on the defensive efforts of the body to counteract neoplastic growth which he divided into three types, sclerotic reactions which produce fibrosis and cut off the blood supply

to the tumor, lymphoid reactions which surround the tumor with lymphoid tissue and prevent the diffusion of “toxic cancerous substances,” and inflammation reactions which is not a defensive reaction but rather an offensive action on the part of the cells. The organism must have a capacity for inflammation in order to successfully counteract cancer.

Dr. DeCourcy remarked on the frequent association between fever and remission, usually brought on by an infection. He speculated that infection and fever stimulate both the inflammation process and thrombosis and since any damage done to the blood supply of a tumor affects the nutrition of the cells, inflammation encourages the death and reabsorption of the tumor. This may be the “reason hemorrhages are frequently associated with regression of tumors. It has been observed that any treatment tending to produce loss of blood has a retarding effect upon the development of neoplasms.”³¹

He recounted the case reported by Mackay³² in which a cachexic woman suffering from terminal breast cancer with pleural effusion suddenly recovered when the fluid was absorbed into her system, and the subsequent experiments of Hodenpyl with ascitic fluid, and suggested that “the remarkable selectivity of the necrotizing effect upon cancer cells exerted by ascitic fluid from a recovered case of cancer” suggests that some substance is present, perhaps protein in nature, that actively fights malignant growths and “points to a lytic action rather than an antitoxic effect.”³³

- In 1950, J. Engelbert Dunphy³⁴ published four case histories. Each provided a different perspective of his view that cancer undergoes “periods of spontaneous arrest or regression alternating with periods of growth, and that this phenomenon is a function, at least in part, of local tissue resistance.”³⁵ He wrote, “The occurrence of spontaneous regressions renders untenable the hypothesis that ‘cancer is a progressive, lawless, autonomous growth dependent upon the host only for its blood supply.’”³⁶ If there are factors that lead to progression of tumors, then “the alteration or withdrawal of these factors . . . can result in dissolution of the tumor.”³⁷

In conclusion he warned that “in the evaluation of new methods of cancer therapy it is obvious that occasional temporary regressions or arrests of tumors cannot be interpreted as evidence of a successful response to a particular agent unless it is consistently observed in many different cases.”³⁸

- In 1952, pathologist Fred W. Stewart presented The Bertner Lecture at the 5th Annual Symposium of The University of Texas M. D. Anderson Hospital. In his presentation on cancer pathology and biological control mechanisms he pointed out that “certain patterns of tumor growth are close duplications of stages of embryonic development, developmental patterns that mature under control” and that “every early placenta looks and for a period acts like a cancer. I like to think of it as a cancer, in the high proportion of cases under control.”³⁹ He stated that spontaneous regressions of established cancer are evidence for the state of biological control and emphasized the importance of viewing cancer growth in this light. He warned about the pitfalls of too heavy a reliance on the new approaches to cancer treatment:

Thinking in the cancer field is perhaps too largely directed to methods of artificial destruction of the cancer cell—either by its radical removal or its chemical destruction. There has not been enough thought given to biological control by the host. Of course the former is easy when the setting is favorable, and we lack all the knowledge to undertake the latter. Still, I am willing to predict that the solution will be the latter, and that it may not be too many decades away.⁴⁰

- Morton and Morton⁴¹ in 1953 published a review paper which presented 17 case histories to support their theory that cancer is a chronic disease. They offered no explanation of the long course of the disease in some patients and warn that “. . . prognosis in terms of survival time in an individual situation should be given cautiously since any case may be well above or below the general average.”⁴² In reviews that appeared later, some of the Mortons’ cases would be cited as examples of spontaneous regression although many of their patients received some form of therapy. If Ikem’s definition of spontaneous remission is accepted, then these cases are examples of long survival of the host body.

- In 1956 in Italy Sirtori and Pizzetti⁴³ published a review of approximately 48 cases from the world medical literature. They found that the tumors most subject to spontaneous regressions were chorion-epitheliomas (20); retinoblastomas (11); neuroblastomas (6); sarcomas (3); and melanomas (3). Their report also included 2 cases of uterine cancer, and 1 case each of liver, pancreas, and a metastatic neoplasm without a primary specified. They hypothesized that four steps are involved in spontaneous regression of malignant tumors: cytolysis, usually caused by removal of blood supply to the tumor; cellular differentiation caused by developmental or hormonal factors; connective tissue activity caused by sclerosis; and defensive activities of the immune system which may result in necrosis.

- The next major literature review was published in 1960 in France, six years before Everson and Cole's and William Boyd's texts on the subject. The French review by J. Fauvet, J. Campagne, A. Chavy and G. Piet⁴⁴ conducted an exhaustive review of the literature from 1866 to 1960, and accepted as authentic 175 cases of spontaneous healing, regression of cancer or complete recovery. Fauvet et al. are the only authors to differentiate among spontaneous healing, regression and recovery. The authors described the differences between the three: For spontaneous healing to have occurred, first there must be absolute certainty that the person had cancer, and have follow-up information, for regression there must be a considerable decrease in the size of the tumor with certainty that what has regressed is not just an inflammatory or edematous phenomenon, and for recovery many years must have passed with no recurrence.

A follow-up report by Fauvet, Roujeau and Piet⁴⁵ in 1964 added 27 new cases to the collection. The authors estimated that they reviewed over 400 cases of possible spontaneous regression out of which they reported that 195 have been published since 1950 and there were only 40 cases published in the preceding 20 years. The authors wrote, "Therefore, the number of acknowledged cases is growing and the notion of spontaneous regression is becoming accepted."⁴⁶

SUMMARY OF CASES OF SPONTANEOUS REGRESSION OF CANCER REVIEWED BY FAUVET, CAMPAGNE, CHAVY AND PIET (N = 202) †

Tumor Type/Site	Cases	Possible Causes of Remission
Oral cavity & digestive organs	37	
stomach	16	laparotomy, wound infection, gastroenterostomy
colon & rectum	10	incomplete operation, ileostomy, fever, pneumonia
liver	1	
pancreas	1	
gall bladder	1	
small intestines	3	ileal resection, colostomy
tongue	2	
mouth	1	mouth wash, pregnancy
lip	2	
Neuroblastoma	17	chickenpox, differentiation, Coley's toxins, biopsy, incomplete removal
Breast	16	wound infection, general infection, erysipelas, ascites, fluid, pregnancy, cachexia, coma induction, typhoid, pleurisy, menopause

SUMMARY OF CASES REPORTED BY FAUVET ET AL. (CONTINUED)

Tumor Type/Site	Cases	Possible Causes of Remission
Genitourinary organs	83	
chorioepithelioma	13	hysterectomy, estrogen
uterus	6	hemorrhage, laparotomy, high fever and urticaria, pregnancy, tubal abortion
cervix	10	fever, incomplete operation
ovary	9	toad venom, laparotomy, ascites
vagina	1	
testis	5	erysipelas
penis	3	erysipelas
prostate	1	stillbesterol
bladder	19	uretero-sigmoidostomy, biopsy, urinary diversion
kidney	16	nephrectomy followed by disappearance of metastases
Bone, connective & soft tissue	17	
bone sarcomas	3	Coley's toxins
soft tissue sarcomas	14	erysipelas, abscess, hot air bath, fever, biopsy
Skin	17	
epitheliomas	6	erysipelas, smallpox, palliative radiation
melanoma	11	incomplete operation, erysipelas, pneumonia, septicemia, regression following pregnancy
Respiratory organs	2	
larynx	1	abscess
lung	1	high fever
Lymphatic & hematopoietic	6	
multiple myeloma	1	hepatitis
lymphosarcoma	5	erysipelas, biopsy
Eye, brain & nervous system	3	
retinoblastoma	2	
brain	1	cerebellar medulloblastoma
Unspecified site	4	biopsy, fever

† The data in this chart is compiled from the papers by J. Fauvet, J. Campagne, A. Chavy and G. Piet, "Guérisons, régressions et rémissions spontanées des cancers," *La Revue du Praticien*, 10 (1960), 2349-2384, and J. Fauvet, J. Roujeau and R. Piet, "Les guérisons et régressions spontanées des cancers," *La Revue du Praticien*, 14 (1964), 2177-2180.

Approximately 50% of the cases (98 cases) occurred in six types of cancer:

- Bladder (19 cases)
- Neuroblastoma (17 cases)
- Hypernephroma (16 cases)
- Stomach (16 cases)
- Breast (16 cases)
- Soft tissue sarcomas (14 cases)

The authors presented a classification of the events which occurred prior to the spontaneous regressions reported in their review:

1. Infections with a high prolonged fever, usually erysipelas, but regressions also have been recorded after smallpox, typhoid fever, pneumonia, wound infections, abscesses, urticaria, and hepatitis.
2. Severe shock to the system such as coma and hemorrhage.
3. Diversion operations (gastric, intestinal and urinary) the authors hypothesize could reduce the apparent volume of the tumor by eliminating edema and infection.

4. Partial excision of the tumor.
5. Exploratory laparotomies with biopsy only.
6. Simple biopsy.
7. Pregnancy has been reported to have both a curative and a detrimental effect on tumors. For example, regressions of malignant melanoma have been reported after pregnancy, regressions of uterine cancer following abortion of a tubal pregnancy.
8. No biological explanation.

In an interpretation of the results of research at the time and observations from their experience the authors proposed a biological theory to explain spontaneous regression. The evidence from organ transplants indicates that the organism resists the transplanted tissue and eliminates it. In the spontaneous regression of cancer it appears that the organism suddenly recognizes the tumor as foreign.

They posed the following research questions:

- Could an infection or post-operative process such as diversion operations alter the immunological mechanisms, specifically the gamma globulins, that exist between the cancer and the host and cause the body to recognize the tumor as foreign?
- Could spontaneous recovery be due to the interaction of two different immunological mechanisms, cellular and humoral, resulting in a change in the blood proteins, such as the gamma globulins?

To test this hypothesis the authors suggested that a tumor should be grafted into an animal while at the same time inoculating the animal with an infection.

- Throughout the 1960s and '70s, possibly stimulated by several reviews that appeared in the literature, many physicians throughout the world published analyses and case histories of spontaneous regression. Reviews appeared in the literature from Germany, Denmark, Italy, and Japan, to name a few. In England in 1962, D. W. Smithers⁴⁷ published an article in which he listed cases of spontaneous regression of retinoblastoma (16 cases), breast cancer (12 cases including 3 from his personal experience), chorion-epithelioma (14 cases), hypernephroma (10 cases), malignant melanoma (8 cases), soft tissue sarcoma (5 cases), and bladder carcinoma (8 cases) with speculations about mechanisms.
- In 1963 Alexander Brunshwig⁴⁸ presented 3 case histories from his personal experience of the previous 8 years; 1 case of uterine cancer, 1 of bladder cancer, and 1 of colon cancer. No therapy was given to these patients once metastases developed. In each case the metastases were biopsied. He briefly discussed possible explanations for spontaneous regression and emphasized the importance of research in this area.
- In 1966, two texts on spontaneous regression appeared, a volume by William Boyd in which he presented brief histories of 98 cases, and a study by two surgeons, Tilden Everson and Warren Cole, who analyzed cases from the medical literature since 1900 and from personal communications.

In his monograph, pathologist William Boyd presented 98 summaries of cases of spontaneous regression "with which I am familiar either from personal experience or in the literature." In the preface to his monograph Dr. Boyd said:

Down through the centuries we read accounts of miraculous cures of this deadliest of disease, but we reject them because of insufficient proof, for miracles no longer occupy the enviable position in happy therapeutic results that they used to do. It was only when biopsy with histological confirmation of the clinical diagnosis became general that 'miraculous cures' could be accepted, and even then there was always the possibility that the pathologist might have been in error.

In recent years a diagnosis of spontaneous regression of cancer has at last become respectable, and reports of such cases are appearing in the literature in ever-increasing numbers.⁴⁹

He suggested that while we do not understand the mechanisms of spontaneous regression, perhaps in the future we will and suggested that “In the meantime, it might be well to follow Brunschwig’s suggestion of establishing a registry for living patients whose histories are acceptable as instances of spontaneous regression.”⁵⁰

**SUMMARY OF CASES OF SPONTANEOUS REGRESSION OF CANCER REVIEWED
BY WILLIAM BOYD (N = 98) †**

Tumor Type/Site	Cases	Possible Causes of Remission
Oral cavity & digestive organs	10	
stomach	3	partial gastrectomy
colon & rectum	3	colostomy, biopsy, fever, wound infection
liver	2	biopsy
gallbladder	1	cholecystectomy
pharynx	1	opiates
Neuroblastoma	15	biopsy, partial excision, palliative radiation, nitrogen mustard
Breast	15	excision of primary, oophorectomy, prolonged arrest
Genitourinary organs	11	
choriocarcinoma	3	hysterectomy
ovary	2	removal of diseased ovary
testis	2	excision of primary
bladder	1	
kidney	3	biopsy, calcification, necrosis
Bone, connective & soft tissue	6	
bone sarcomas	2	fever
soft tissue sarcomas	4	biopsy, fever
Skin	11	
malignant melanoma	11	prolonged arrest, delayed metastases, partial excision, pregnancy, blood transfusion, fever, infection
Respiratory organs	5	
larynx	1	biopsy
lung	4	fever, biopsy, pleural effusion
Eye, brain, nervous system & endocrine glands	23	
retinoblastoma	17	removal of one eye
brain	2	
thyroid	4	palliative radiation of metastases
Metastatic: unknown primary site	2	biopsy, ascites

† Data compiled from the monograph by William Boyd, *The Spontaneous Regression of Cancer* [Charles C. Thomas, Publisher, 1966].

Boyd stated in his conclusion that there is no one cause of spontaneous regression, just as no one event causes cancer and suggested that spontaneous regression may occur very frequently. For example little information is known about the occurrence or the rate of regression of what is called latent cancer. The work of Franks⁵¹ who found that on autopsy of 220 men who died of various causes, 36% of them had evidence of prostate cancer. In men in their 60s and 70s, he found one-third had evidence of prostate cancer and in men over 80, 50%, but they didn’t show clinical signs. Studies of the natural history of latent cancers such as these might point to some of mechanisms of spontaneous regression.

He suggested that a second area of study that might prove fruitful would be the investigation of the causes of regression in the four kinds of cancer that regress most frequently: neuroblastoma, choriocarcinoma, malignant melanoma and hypernephroma.

Based upon the limited knowledge of the phenomenon, Boyd believed there were only three possible causal factors that might help explain spontaneous regression that are known at present: 1. effects of therapy; 2. hormonal influences; and 3. bodily immune responses, and, for the study of biological mechanisms of spontaneous regression, it is most important to concentrate on the concept of resistance, both on the part of the host and the tumor. Tumors are not autonomous, beyond control. The wide fluctuations in the growth rate of tumors is due primarily to changes in the resistance of the organism not to changes in virulence of the tumor. It is the concept of control that is central to the phenomenon of spontaneous regression.

SPONTANEOUS REGRESSION OF CANCER BY TILDEN C. EVERSON AND WARREN H. COLE

• Prior to the publication of their classic text on spontaneous regression of cancer in 1966 Tilden Everson and Warren Cole published two preliminary reports on their analysis of the world's medical literature, one in 1956⁵² and another written by Everson alone in 1964⁵³. In their 1956 report, out of the over 600 cases published or obtained by personal communications, Everson and Cole considered only 47 cases to have adequate documentation to be considered spontaneous regressions. In a report by Tilden Everson in 1964, the number of cases accepted had grown to 130. This was due not only to the increase in the number of reported cases analyzed in the 8 intervening years (from 600 to 1000 cases), but also to an increase in the number of categories of clinical evidence acceptable for inclusion, from the first two categories below to all four. In order to be accepted as spontaneous regression the clinical evidence of the case must conform to the criteria of one of the following categories:

1. Regression of a primary tumor.
2. Regression of a metastatic tumor with histological confirmation of malignancy of the metastatic tumor.
3. Regression of metastatic tumor without histological confirmation of malignancy of the metastatic tumor.
4. Regression of presumptive metastases as diagnosed by x-rays.

In their 1966 text, the number of cases that met the criteria they defined for acceptance increased from 130 to 182. The inclusion of the two additional categories above made regression of pulmonary metastases of hypernephroma acceptable for inclusion which added 21 new cases. An additional 19 cases of neuroblastoma, 19 cases of choriocarcinoma, 14 cases of malignant melanoma, 7 cases of soft tissue sarcoma and 5 cases of bladder cancer were also added to the totals. In addition to these 182 cases Everson and Cole presented 9 cases of chorioadenoma destruens, 9 cases of hydatidiform mole, 1 case of ovarian papillary cystadenoma, and one case of fibromatosis, tumors considered to be either benign or uncertain in their behavior.

Two additional categories, prolonged arrest of cancer and delayed metastasis or recurrence of cancer, were added to the list above and representative case summaries of these two categories were presented in a separate section. Although these two additional categories, according to the authors, do not represent evidence of spontaneous regression per se, they indicate possible biological control of cancer and may be closely related to spontaneous regression.

Everson and Cole commented that "Spontaneous regression actually may be a poor term to describe this phenomenon, since it is not implied that there is no cause for the regression but rather that the regression is due to internal [Everson and Cole's emphasis] rather than external factors . . . perhaps the most suitable term for this phenomenon might be biologic regression of cancer."⁵⁴ They listed seven possible factors that may be of importance in causing the spontaneous regression of cancer. These included:

1. *Endocrine influences.* These influences may be responsible for some of the spontaneous regressions of hypernephromas, malignant melanomas, ovarian, testicular, breast, and thyroid carcinomas.
2. *Fever and infection.* These factors have been reported associated with spontaneous regression since the middle of the nineteenth century and continue to be associated with spontaneous regression.

3. *Allergic or immune reactions.* The cause of a spontaneous regression has been reported to be due to an immune or allergic response when no other cause can be found. This may explain some of the reported regressions of choriocarcinoma and malignant melanoma.

4. *Interference with nutrition of the cancer.* Interference with the blood supply after incomplete surgery has been reported as a possible cause of spontaneous regression which may explain some of the regressions of neuroblastomas.

5. *Removal of carcinogenic agents.* This factor may possibly be responsible for the regressions of cases of cancer of the bladder.

6. *Unusual sensitivity to usually inadequate therapy.* It is possible that some regressions are due to unusually favorable responses to medication or small amounts of radiation.

7. *[In]complete surgical removal of cancer.* After a partial removal of a tumor the remaining tumor spontaneously regresses. It is possible that the residual tissue was inflammatory rather than malignant but in cases with good histological information this idea can be ruled out.

8. *Incorrect histologic diagnosis of malignancy.* This has been the most frequent explanation for unexplainable spontaneous regression. A diagnostic error in some cases can result in the inclusion of reports that are not a true spontaneous regression.

SUMMARY OF CASE REPORTS OF SPONTANEOUS REGRESSION OF CANCER CITED BY EVERSON AND COLE (N = 202) †*

Tumor Type/Site	Cases	Possible Causes of Remission
Oral cavity & digestive organs	16	
stomach	4	excision of primary (1), gastroenterostomy (3)
colon & rectum	8	abscess (2), biopsy (1)
liver	2	biopsy (1)
pancreas	1	biopsy (1)
tongue	1	
Neuroblastoma	29	Coley's toxins (4), biopsy (15), partial excision (4), palliative radiation (4), varicella infection (1), HN ₂ (1), triethylene-melamine (1)
Breast	6	menopause (1), excision of primary (1)
Genitourinary organs	84	
choriocarcinoma	19	testosterone (1), excision of primary (5), partial excision (1), palliative radiation (5), chlortetracycline (1)
uterus	4	excision of primary (2)
ovary	7	removal of diseased ovary (2), removal of both ovaries (3), biopsy
testis	8	excision of primary (2), radiation (1)
bladder	13	transplantation of ureter, cystectomy (12)
kidney	33	testosterone (1), prednisone (1), progestational agent (3), excision of primary (24), biopsy (1)
Bone, connective & soft tissue	19	
bone sarcomas	8	Coley's toxins (1), biopsy (1), palliative radiation (1)
soft tissue sarcomas	11	hot air bath (1), Coley's toxins (2), amenorrhea (1), excision of primary (2), biopsy (4), partial excision of primary (4), palliative radiation (1), fever (3), wound infection (1)
Skin	19	
malignant melanoma	19	tagged antibodies (1131) (1), blood transfusion (3), antirabies inoculations (1), hot air baths (1), delivery of child (3), excision of primary (6), excision of metastasis (1), palliative irradiation (3), abscess (1)

SUMMARY OF CASES REPORTED BY EVERSON AND COLE (CONTINUED)

Tumor Type/Site	Cases	Possible Causes of Remission
Respiratory organs	3	
larynx	1	biopsy
lung	2	biopsy (2)
Thyroid	2	biopsy (1)
Metastatic: unknown primary site	4	fever, biopsy, empyema, jaundice
Total Malignant Cases	182	
Neoplasms of uncertain behavior & benign neoplasms	20	
chorioadenoma destruens	9	disappearance of pulmonary metastases following hysterectomy, removal of hydatidiform mole, stilbestrol
hydatidiform mole	9	disappearance of pulmonary metastases following removal of mole
ovarian papillary cystadenoma	1	menopause, inflammation, celiotomy, removal of ascitic fluid
fibromatosis	1	biopsy, excision
Total Cases	202	

† number of cases includes benign neoplasms and neoplasms of uncertain behavior; data compiled from Tilden C. Everson and Warren H. Cole, *Spontaneous Regression of Cancer* [W. B. Saunders Co., 1966].

* number in parentheses following possible causes indicates number of cases; from Warren H. Cole, "Spontaneous regression of cancer: The metabolic triumph of the host?" *Annals of the New York Academy of Sciences* 230 (1974), 128-129.

Sixty-eight percent of the cases (124 cases) occurred in six types of cancer:

- hypernephroma (33 cases)
- neuroblastoma (29 cases)
- malignant melanoma (19 cases)
- choriocarcinoma (19 cases)
- bladder (13 cases)
- soft tissue sarcomas (11 cases).

DISTRIBUTION OF MALIGNANT CASES (N = 182) IN FIVE-YEAR PERIODS REPORTED BY EVERSON AND COLE*†

The distribution of cases reported in their text demonstrates a much higher incidence reported for the years 1950-1964 than in previous years. The authors remarked that this figure may be misleading since there has been greater interest in, and more reporting of, spontaneous regression in recent decades.

Five-Year Period	Cases	Five-Year Period	Cases
1900-1904	1	1935-1939	10
1905-1909	3	1940-1944	6
1910-1914	2	1945-1949	12
1915-1919	3	1950-1954	33
1920-1924	3	1955-1959	49
1925-1929	5	1960-1964	51
1930-1934	2	1965	2

* 6 cases reported in Everson and Cole's addendum are included, 1 from 1960, 3 in 1964 and 2 in 1965.

† Adapted from an article by Warren H. Cole "Spontaneous regression of cancer: The metabolic triumph of the host?" *Annals of the New York Academy of Sciences* 230 (1974), 112.

DURATION OF SPONTANEOUS REGRESSION IN CASES REPORTED BY EVERSON AND COLE (N = 176)†

It is difficult to evaluate the duration of spontaneous regression because many of the reports do not contain long-term follow-up of the patients. Everson and Cole reviewed the case reports in their text to determine duration of regression. The following chart provides information on the duration of the regression in those patients where the information was available.

Number of Cases	Percent of Total Cases	Estimated Duration
28	15.9%	no information
21	11.9%	< 6 months
10	5.7%	6 to 12 months
25	14.2%	1 to 2 years
35	19.9%	2 to 5 years
35	19.9%	5 to 10 years
22	12.5%	10 years or more

† based on information in Warren H. Cole, "Spontaneous regression of cancer: The metabolic triumph of the host?" *Annals of the New York Academy of Sciences* 230 (1974), 112.

Everson and Cole, in their conclusion, discussed the significance of the spontaneous regression data.

1. The existence of spontaneous regression of cancer, in at least some cases, supports the concepts of biologic control of cancer and reinforces the hope that a more satisfactory method of treating cancer than surgery or irradiation may be found.
2. The occurrence of spontaneous regression of cancer demonstrates need for caution in assessing the value of chemotherapeutic and unorthodox therapeutic measures in isolated 'cures' of cancer.
3. The possibility of spontaneous regression of cancer must be considered in the evaluation of the prognosis of certain cancers.
4. The remote possibility of spontaneous regression of cancer may be of some therapeutic value in the patient with cancer that is not amenable to surgical or radiation treatment.⁵⁵

Everson and Cole stated that "It must be recognized, of course, that possible cases of spontaneous regression of cancer will only be found either among those patients who foolishly refuse to accept orthodox methods of cancer therapy or among those patients whose cancer is too far advanced for the use of present accepted methods of cancer therapy."⁵⁶ While the authors recognized that the occurrence of spontaneous regression in some areas while the tumor grows unabated in others or where temporary regressions of short duration occur are of questionable benefit to the patient, they advocated the study of these cases may shed some light on the biological mechanisms involved. "(It must be emphasized, however, that the statistical possibility of spontaneous regression occurring in any single case of cancer is so extremely small that any patient would be most foolish to reject orthodox methods of treatment in the hope that his cancer would regress spontaneously)."⁵⁷

FIRST—AND ONLY—WORLD CONFERENCE ON SPONTANEOUS REMISSION

• Numerous authors throughout the 1960s and '70s reported individual cases of spontaneous regression in the world's medical literature, but the next major evaluation of spontaneous regression did not take place until May of 1974 when the first world conference on the subject took place at Johns Hopkins University School of Medicine.⁵⁸ Its purpose was to determine:

1. Whether or not spontaneous remission occurs at all.
2. If so, what is its mechanism of action?
3. Does that mechanism suggest any new therapeutic approach?

A report of the conference suggested that answers were difficult to find since at that time access to the case histories was poor. Not many cases had been reported then, though Medical World News acknowledged that “unverified claims of ‘miracle cures’ probably number thousands.”⁵⁹

The presentations at the conference were divided into three broad areas: clinical documentation, mechanisms of action, and speculations, hypotheses and theoretical considerations. Dr. Edward Lewison, one of the conference organizers, in his opening remarks said, “The purpose of this *Conference on Spontaneous Regression of Cancer* is to listen more closely and more attentively to those ‘whispers of nature,’ whereby a rare and extraordinary patient with clinically confirmed cancer responds in an unusual and exceptional way without adequate treatment.”⁶⁰

In his opening address, Warren H. Cole presented the largest body of information on spontaneous regression when he spoke on his collaborative survey with Tilden Everson of 176 cases of spontaneous regression. Their definition of regression as “a partial or complete disappearance of a tumor in the absence of treatment which ordinarily is considered capable of producing a regression” was faulted by Cole since it was claimed that the definition applies to cases that could “quite plausibly be explained by known mechanisms.”⁶¹ Dr. Cole presented nine possible causes of spontaneous regression in the series of 176 cases: immunologic factors, elimination of a carcinogen, body response to operative trauma, hormone factors, role of irradiation, infection and/or fever, drugs, interference with the blood supply and severe malnutrition. He also examined data that could be indirectly related to the phenomenon: hormone therapy, immunoglobulins, immune reaction, and enzymes that have been reported to interfere with tumor growth.

Following Dr. Cole, the next several presenters focused on specific cancer types and reported cases of spontaneous regression either from their own experience or from reviews of the literature. Among the types of cancer represented were genitourinary cancers, breast cancer, gynecological cancers, lung cancer, leukemias, lymphomas including Burkitt’s lymphoma, neuroblastoma, sarcomas, choriocarcinoma, and malignant melanoma. Dr. Hugh Stephenson in his presentation implored physicians to create and report detailed histories of patients who exhibit spontaneous regression of cancer in the hope of developing a systematic body of information. Dr. Peter Wiernik presented a review of spontaneous remission of hematological malignancies and pointed out that in acute leukemias most remissions were of short duration and associated with bacterial infections, in lymphomas regressions were of substantial duration and frequently associated with viral infections, and in chronic lymphocytic leukemia remissions have been of significant duration and associated with occurrence of new primary carcinomas in one-third of the cases.

The explanation for spontaneous regression that was favored by most attendees was immunological responses, with most of the papers presented at the conference reviewing some aspect of immunological mechanisms. Dr. Horst Schirmer presented information on regression after surgery and said the mechanism could be explained by immunological processes. Dr. Audrey Evans presented a report on spontaneous regression of neuroblastoma and concluded that since neuroblastoma occurred in children less than 6 months of age whose immune systems were immature that as the child matured the maturing immune mechanisms could overcome the tumor. Dr. Roy Hertz, in his presentation on choriocarcinoma, concluded that since this type of cancer originated in embryonic cells which are foreign to the host, the immune response would be strong. Dr. Larry Nathanson presented data that showed regression of malignant melanoma after immunological therapy. Drs. Holmes, Morton, Eilber, Golub and Sulit presented their research on immunotherapy in malignant melanoma, Drs. Klein, Rosner, Holtermann, Stoll and Song presented information on antigen reactions, and Dr. George Klein presented his views on immune surveillance. In the last session where theoretical speculations were considered, the Hellströms presented results from their research on tumor immunity.

This heavy concentration on immunological approaches was disappointing for physicians who attended the conference hoping that new approaches to cancer therapy might be explored.

Immunologist David Weiss presented an alternate view. In his view the neoplastic process is only in part immunologic, and any immunological mechanism must be coupled with an understanding of host-parasite relationships, that is, one must study the host, the tumor, and the environment as dynamic interconnected parts of the neoplastic process in order to determine mechanisms of spontaneous regression. He included in the environment not only elements outside the host but also those elements inside the host, “the internal tissue environment as it is shaped by genetic potential, sex, age, and the physical and psychological responses to extrinsic stimuli.”⁶²

He suggested that the numerous reports of spontaneous regression after bacterial infections may provide important clues to the interaction of the host, the cancer and the environment. Possible mechanisms of action that might explain how bacterial infections can cause regressions include the possibility that contact with bacterial antigens may “hyperimmunize” against tumor cells, or that the substances produced by the host to counteract the effects of the infection may also attack tumor cells, or perhaps the inflammatory process that is directed at the bacterial microbe may also affect the tumor cells. A focus on the relationships between host, tumor, and environment could open up new avenues for research and allow researchers to view their results in a new way.

Dr. Lewis Thomas also suggested that one should look to clues in the cases of spontaneous regression after bacterial infections and Coley’s toxins. The presumed mechanism of action usually accepted for Coley’s toxins, that of the action of bacterial endotoxins to cause hemorrhagic necrosis, could be one mechanism of spontaneous regression.

Dr. Rene Matrovito during a discussion session at the conference introduced cases where cancer developed after a psychological trauma. He said that “almost no cancer patients have schizophrenia,”⁶³ and mentioned the references to spontaneous regression following religious conversion and prayer.

Drs. Sindelar and Ketcham suggested that endocrine factors, psychologic factors, trauma and stress, diversion of urinary and fecal streams, infection and fever, and exposure of patients to diagnostic procedures such as x-rays, radionuclide scans, changes in diet, administration of drugs, and operative manipulations may be some of the factors that could cause spontaneous regression following surgery. Regarding psychological factors they suggested that the trauma of hospitalization, diagnosis of cancer, and surgery could produce emotional effects that may change hormone and metabolic balance. “These influences may alter host responsiveness such that certain tumors might find a metabolic environment that was no longer suitable for growth.”⁶⁴

In his concluding address, Dr. G.J.V. Nossal summarized the material presented and called for the further study of all factors that might have an impact on spontaneous regression.

- In *Mind and Cancer Prognosis* published in 1979, Basil Stoll suggested that while cases of spontaneous regression are reported in only about 20 patients annually the actual number of regressions may be much larger. He gave several reasons why he believed the incidence is likely to be much larger:

1. Cases where the tumor shrinks and then regrows in a few months are less frequently reported even though partial, temporary regression is part of Everson and Cole’s definition.
2. Slow shrinkage of a tumor over a period of several months is probably also underreported.
3. Sometimes metastases shrink at one site and remain unchanged at others. These cases are also probably underreported.
4. Spontaneous regression may account for some of the remissions reported by unorthodox methods of treatment.
5. In places other than large hospitals the diagnostic and histopathological detail may not be available or detailed enough to allow confirmation of spontaneous regression.

Dr. Stoll reviewed the proposed mechanisms that have been reported to account for spontaneous regression. Among the mechanisms discussed are differentiation and maturation of tumors that arise from fetal cells in younger patients such as neuroblastoma, Wilm’s tumor, and embryonal cancer of the

testis, and psychophysiological factors. If there are no other explanations, spontaneous regression “is usually ascribed to heightened host resistance—immunological or endocrinological. . . . If these are the major mechanisms for spontaneous regression, psychological triggering factors may be involved in some cases, because both immunological and endocrinological changes can be triggered off by cerebral cortical activity through the mediation of the hypothalamic centres.”⁶⁵

- Two reviews appeared in 1982, one in England and one in Germany. In *Prolonged Arrest of Cancer*, a monograph edited by Basil Stoll, Dr. C.I.V. Franklin divides his review article into six sections: adult cancer, childhood cancer, leukemia and lymphoma, in situ cancer of the cervix, possible mechanisms and incomplete regression. He suggests that only the most dramatic and long-lasting cases are reported while less dramatic regressions or fluctuations in growth rates occur more frequently and are overlooked. “One reason for this is the reluctance on the part of orthodox practitioners to report cases of apparent regression for which there is no obvious scientific explanation.” In his comments on Everson and Cole’s review of 176 cases, he remarked that “60% of the regressions lasted more than two years, with many over ten years. If the same criteria were applied to regression following hormonal or cytotoxic chemotherapy, response rates may not be much greater than the reported incidence of spontaneous regression!”⁶⁶

In the section on adult cancer, he briefly reviewed the literature on kidney cancer, melanoma, choriocarcinoma, bladder cancer and bone tumors. He presented information on testicular cancers from both the literature and from personal observations, and briefly mentioned cases of lung cancer and breast cancer.

In his section on childhood cancer he commented that solid tumors in childhood differ considerably from that of adults and may provide some mechanisms on the arrest of tumor growth. He reported evidence from studies of neuroblastoma, Wilm’s tumor and retinoblastoma. Leukemias and lymphomas were not reviewed by Everson and Cole presumably because of the natural fluctuations in their growth rates. However, Dr. Franklin included these hematological malignancies in his review and reported that according to Diamond and Luhby⁶⁷, before effective chemotherapy, complete spontaneous remission of short duration occurred in as high as 4.5% of their 300 patients with childhood leukemia, specifically acute lymphoblastic leukemia. In most of these cases the remission was preceded by an acute infection.

He included in his review of possible mechanisms infections, endocrine factors and psychological factors. About psychological factors he said, “The mind exerts an influence over the body and its internal environment in ways that are not understood”⁶⁸ and cited the case of a nun with pancreatic cancer who recovered following biopsy and the prayers of the Mother Superior,⁶⁹ and Anslie Meares⁷⁰ reported of a case of metastatic osteogenic sarcoma that was controlled with meditation.

Dr. Franklin included in his review cases of incomplete regression which he felt are important to the study of spontaneous regression and are frequently excluded from consideration. He also suggested that research should be directed to understanding the mechanisms of regression of benign tumors.

- In a 1982 article published in Germany Dr. Erwin Theiss⁷¹ reviewed the work of Everson and Cole and then briefly reported cases and reviews of spontaneous regression from the European literature, including in his review cases from Germany, Austria, Denmark, Finland, Hungary, the Netherlands, England, and France. For example, Derra and Elmendorff⁷² found 90 cases of inoperable cancer in elderly people who lived over five years, although only 26 were histologically verified. Other cases from Europe reviewed by Theiss were single case reports. He also reviewed cases where psychospiritual factors were thought to play a role although he does not present any explanation for these reports.

- Dr. Jaylene Kent and associates⁷³ published a review paper in 1989 with a different approach to understanding spontaneous remission. While most papers published on the subject speculate on possible biological mechanisms, mostly immunological, and report cases with a medical approach, Kent’s paper focused on research in psychospiritual areas that might influence spontaneous remission. Most of the reports found in the medical literature focused on diagnostic and treatment information and present very little, if any, information about the psychological or life circumstances surrounding the patient.

Kent et al. speculated that evidence from psychoneuroimmunology would indicate that psychological and emotional factors together with biological factors may affect immune function and disease resistance, and by studying these factors along with genetic, endocrine, nervous and immune system interactions an understanding of disease incidence and progression can be found. Much research in this area has focused on the effects of negative emotions and stress on the immune system. Stressful life events such as death of a spouse⁷⁴ or divorce⁷⁵ have been shown to weaken immune function. Positive emotions, relaxation, self-mastery and hypnosis techniques have been supported by research and anecdote and have been shown to have positive effects on health. Kent and associates believed that spontaneous remission is a natural phenomenon with unknown causes. They suggested that “beliefs, coping style, and emotions may play a part in spontaneous remission by modulating immune functioning.”⁷⁶

- Dr. Rose Papac⁷⁷ reported 10 cases of spontaneous regression of cancer, 8 from her clinical experience and 2 in which she was not directly involved, in a paper published in 1990. These cases were 2 cases of malignant melanoma, 2 cases of pulmonary metastases from renal cell carcinoma, 1 case of multiple metastases from a lung carcinoma, 1 case of multiple myeloma, 1 case of liver metastases from a colon carcinoma, 1 case of myelomonocytic leukemia, 1 case of liver metastases from a gastric carcinoma, and 1 case of chronic lymphocytic leukemia. In 1 case, a case of myelomonocytic leukemia, Dr. Papac had been in communication with the patient since 1967. (He is alive and well at the time of this writing.) She briefly reviewed mechanisms of regression that have been reported in the literature, among them immune modulation, infection, hormonal factors, trauma and psychological factors. Of psychological factors she said, “Psychological factors are of interest since it is postulated that metabolic aspects of emotional reactions could influence the growth of tumors.”⁷⁸

Her speculations on mechanisms that might be involved in spontaneous remission focused on the advances in research that have shown that the neoplastic process follows a number of steps which start with oncogene expression and transformation of normal cells to neoplastic ones. The process culminates with proliferation and metastasis. Papac speculated that spontaneous regression may occur as a result of “suppression of oncogene activation, activation of suppressor genes, mutation to a lethal variant or depletion of growth factors or development of an unfavorable microenvironment. . . .”⁷⁹ It is well established that immune and hormone modulation and induction of differentiation, as in the case of neuroblastoma, are mechanisms of spontaneous regression of cancer.

- In 1990, G. B. Challis and H. J. Stam⁸⁰ conducted a literature review and analysis of reports of spontaneous regression of cancer from 1900 to 1987. No case reports were included. The world literature was reviewed from 1966 to 1987 and added to those cases already reviewed by Boyd and Everson and Cole. The criteria for inclusion were those established by Everson and Cole with the exception that Challis and Stam included leukemias and lymphomas in their analysis. They stated, “We can therefore provide a review of the literature from 1900 to 1987 with the exception that prior to 1966 no cases of lymphoma or leukemia were included by either Boyd or Everson and Cole. In addition, Everson and Cole omitted cases of retinoblastoma.”⁸¹

Searches conducted manually and by computer found 1,199 articles pertaining to the subject. The authors excluded 52 articles written in a language other than English (out of 220 articles in languages other than English) that could not be located; animal studies (N = 370); general discussions; reviews of previously published works or letters; editorials or research proposals (N = 475); articles which claimed spontaneous regression of cancer although standard medical treatment was used (N = 119); and those where “an experimental procedure or manipulation was used to deliberately initiate or cause the regression (N = 55).”⁸² Fourteen articles which accounted for 6,136 cases of regression were also excluded due to lack of “sufficient, histologic evidence of both the presence and subsequent regression of individual neoplasms.”⁸³

Out of the 1,199 articles referenced in *Index Medicus* and *Cancer Lit* reviewed by Challis and Stam, 265 articles accounting for 505 case studies between 1966 and 1987 are listed in the following table.

SUMMARY OF CASE REVIEW OF SPONTANEOUS REGRESSION OF CANCER BY
CHALLIS AND STAM (N = 505) †

Tumor Type/Site	Cases	Tumor Type/Site	Cases
Oral cavity & digestive organs	43	Respiratory organs	29
stomach	10	lung	18
colon & rectum	10	bronchi	7
liver	10	larynx	4
pancreas	3	Lymphatic & hematopoietic	124
intestines	1	lymphosarcoma	1
adenocystic carcinoma	5	leukemia	53
squamous cell carcinomas	3	lymphoma	68
nasopharynx	1	Hodgkin's disease	2
Neuroblastoma	42§	Eye, brain, nervous system & endocrine	40
Breast	22	retinoblastoma	33
Genitourinary organs	94	malignoma of the sclera	1
chorioepithelioma	1#	brain	4
uterus	2	thyroid	1
cervix	0	adrenal gland	1•
ovary	1	Metastatic: unspecified primary site	10
testis	16	Benign neoplasms	3
bladder	6*	cardiac tumors	1
kidney	68	osteoblastoma	1
Bone sarcomas	3	osteochondroma	1
Soft tissue sarcomas	1	atypical Hurthle cell adenoma	•
Skin	81	Neoplasms of uncertain behavior	13
squamous cell & epitheliomas	5	Merkel's cell tumor	1
malignant melanoma	69	hemangioendothelioma	2
Kaposi's sarcoma	7	Bowen's disease (vulva)	6
		Bowen's disease (penis)	4
Total			505

† Data from G.B. Challis and H. J. Stam, "The spontaneous regression of cancer: A review of cases from 1900 to 1987," *Acta Oncologica* 29(5) (1990), 545-550.

§ Contains one case of sympathoblastoma.

• Challis and Stams listed one case of adrenal cancer without cell type.

* Includes 2 cases of cancer of the urethra.

Listed as cancer of the endometrium.

Challis and Stam's survey of cases reveal possible mechanisms although most of the authors who have reported cases of spontaneous regression have not discussed the possible mechanisms involved. Host resistance is frequently reported as a cause of regression primarily caused by immunological and hormonal mechanisms. Other biological mechanisms reported are operative trauma, necrosis, and infection. Psychological mechanisms are the only ones reported that are not biological, and the information in this area is limited. Challis and Stam speculated that the reason for such limited information in this area may be a result of the fact "that no physician was willing to risk his/her reputation by reporting a case of spontaneous regression he/she felt was due to a psychological method."⁸⁴ In the popular literature, however, there are many reports of psychological techniques that have been reported to have a positive effect on cancer. In their summary, Challis and Stam concluded that while cases of spontaneous regression continue to appear in the medical literature there is no solid body of evidence that explains the occurrence of this phenomenon.

CASES OF SPONTANEOUS REGRESSION OF CANCER IN LITERATURE REVIEWS: 1918-1993
A summary of cases from reviews in the medical literature is presented in the following table:

Tumor Type/Site	Rohdenburg 1918	Fauvet et al. 1960, 1964	William Boyd 1966	Everson & Cole 1966	Challis & Stam 1990	O'Regan & Hirshberg 1993
Oral cavity & digestive organs	27	37	10	16	43	25
esophagus	0	0	0	0	0	1
stomach	8	16	3	4	10	6
colon & rectum	7	10	3	8	10	4
liver	1	1	2	2	10	3
pancreas	0	1	0	1	3	1
gallbladder	2	1	1	0	0	1
small intestines	0	3	0	0	1	0
adenocystic carcinoma	0	0	0	0	5	1
mouth	9	5	1	1	4	3
Neuroblastoma	0	17	15	29	42*	30
Breast	39	16	15	6	22	22
Genitourinary organs	69	83	11	84	94	58
chorioepithelioma	10	13	3	19	1	3
uterus	42	6	0	4	2	2
cervix	10	10	0	0	0	3
ovary	3	9	2	7	1	3
vagina	1	1	0	0	0	0
testis	1	5	2	8	16	2
penis	0	3	0	0	0	1
prostate	0	1	0	0	0	0
bladder	1	19	1	13	6	2
kidney	1	16	3	33	68	42
Bone sarcomas	5	3	2	8	3	6
Soft tissue sarcomas	21†	19†	4	11	2†	7
Skin	15	17	11	19	82	27
squamous cell & epitheliomas	13	6	0	0	5	5
malignant melanoma	4#	11	11	19#	70#	14#
Kaposi's sarcoma	0	0	0	0	7	2
Respiratory organs	0	2	5	3	29	8
lung	0	1	4	2	25	8
larynx	0	1	1	1	4	0
Lymphatic & hematopoietic	0	1 §§	0	0	123	30
leukemia	0	0	0	0	53	17
lymphoma	0	0	0	0	68	13
Hodgkin's disease	0	0	0	0	2	0
Eye, brain & endocrine	0	3	19	0	38	9
retinoblastoma	0	2	17	0	33	7
brain	0	1	2	0	4	2
thyroid	0	0	4	2	1	0
Unspecified primary site	7	4	2	4	10	0
Total (malignant cases)	185	202	98	182	489	216

* includes one case of sympathoblastoma.

† includes lymphosarcoma: Rohdenburg and Fauvet et al. report 5 cases; Challis & Stam review 1 case.

includes melanoma of the choroid: Everson & Cole and O'Regan & Hirshberg report 3 cases each; Challis & Stam review 1 case of malignoma of the sclera; Rohdenburg reports 2 cases of sarcoma of the eye (possibly melanoma of the choroid).

§§ includes 1 case of multiple myeloma.

CASES OF SPONTANEOUS REGRESSION OF CANCER IN LITERATURE REVIEWS: 1918–1993 (CONTINUED)

Tumor Type/Site	Rohdenburg	Fauvet et al.	William Boyd	Everson & Cole	Challis & Stam	O'Regan & Hirshberg
	1918	1960, 1964	1966	1966	1990	1993
Benign neoplasms	NR	NR	NR	NR	4~	35
gastric polyps	NR	NR	NR	NR	NR	4
colon polyps	NR	NR	NR	NR	NR	2
liver adenoma	NR	NR	NR	NR	NR	2
mesenchymal hamartoma	NR	NR	NR	NR	NR	1
pulmonary leiomyoma	NR	NR	NR	NR	NR	1
cardiac tumors	NR	NR	NR	NR	1	3
osteoblastoma	NR	NR	NR	NR	1	2
osteochondroma	NR	NR	NR	NR	1	4
fibromatosis	NR	NR	NR	1	NR	6
desmoid tumors	NR	NR	NR	NR	NR	3
hemangiomas	NR	NR	NR	NR	NR	4
atypical Hurthle cell adenoma	NR	NR	NR	NR	NR	1
cystic hygromas	NR	NR	NR	NR	NR	1
lymphangioma	NR	NR	NR	NR	NR	1
Neoplasms of uncertain behavior	NR	NR	NR	NR	13	10
hemangioendothelioma	NR	NR	NR	NR	2	3
Bowen's disease	NR	NR	NR	NR	10§	1§
chorioadenoma destruens /hydatidiform mole	NR	NR	NR	18	NR	3
neurofibromatosis	NR	NR	NR	NR	NR	2
phaeochromocytoma	NR	NR	NR	NR	1+	1
ovarian papillary cystadenoma	NR	NR	NR	1	NR	NR
Totals	185	202	98	202	505	261

~ includes 1 case of Merkel cell tumor.

§ Challis & Stam review 6 cases of Bowen's disease of the vulva and 4 cases of Bowen's disease of the penis; O'Regan & Hirshberg report 1 case of Bowen's disease of the vulva.

+ Challis & Stam include 1 case of adrenal cancer without indication of type.

NR: not reported.

Reviews of cases of spontaneous regression vary considerably. For example, Fauvet included 16 cases of hypernephroma, Everson and Cole reported 31 cases, William Boyd included only 3, Challis and Stam reviewed 68 cases, and we reported 42. Fauvet and Boyd agreed in the number of cases of neuroblastoma reported, 17 and 15 respectively. Our number of reports of neuroblastoma, 30 cases, agreed with Everson and Cole who reported 29. In breast cancer, Boyd and Fauvet were in agreement reporting 15 and 16 cases respectively, while Rohdenburg reported a considerably greater number, 39 cases, and Everson and Cole considerably fewer cases with 6. Boyd reported 17 cases, Fauvet reported 2, Challis and Stam reviewed 33 cases, we reported 2 cases, and Everson and Cole excluded retinoblastoma from their study. Rohdenburg reported 42 cases of regression of uterine cancer, while the later reviews reported many fewer cases. The differences in reports may be a result of any of the following:

1. Advances in treatment procedures.
2. Diagnostic procedures.
3. Changes in methods of reporting.
4. Knowledge of carcinogenesis.
5. Differences in definitions of spontaneous regression.
6. Differences in inclusion criteria.
7. Increased numbers of cases reported over time.
8. The data collection process. (Until recently, references had to be sought by letter, telephone and searches through the literature in the medical libraries.)

My present purpose is not to vaunt a new remedy but to state a fact—that cancer, even when advanced in degree and of long duration, may get better, and does sometimes get well. There is cure of cancer, apart from operative removal. These cases, rare though they be, are the sun of our hope.

1910: Sir Alfred Pearce Gould, *The Bradshaw Lecture on Cancer. Lancet*, 2: 1665.

POSSIBLE BIOLOGICAL MECHANISMS OF REMISSION: IMMUNOLOGICAL FACTORS

In the 1960s and '70s the focus of work in cancer research moved into the laboratory in an attempt to understand the cancer process and in that way find a cure. The primary focus of the laboratory work has been on immunological factors associated with tumor growth and regression. Warren Cole, in a paper published in 1976, said:

After years of thought concerning the cause of this phenomenon [spontaneous regression], this author is convinced that most of the cases are examples of development of an immunologic process, and if we knew the explanation of the regression, we would be able to develop a method for regression of many types of human cancer.⁸⁵

Although cancer researchers have always assumed there are at least some immunological control mechanisms involved in the development and regression of tumors, not until a better understanding of immunology had been achieved could researchers study in depth the biology of cancer. Early work in the 1940s and '50s laid the foundations by showing that animals produced antibodies to tumors and developed an immunity to chemically induced tumors after regression. In 1957, Prehn and Mann⁸⁶ found tumor specific antigens in chemically induced tumors. Later, the Hellströms and associates⁸⁷ found that nearly all transplanted animal tumors contained tumor specific transplantation antigens.

Work in humans showed that some patients with various types of cancer produced circulating antibodies to their tumors, and those that did not produce the antibody had more advanced disease.⁸⁸ The Hellströms⁸⁹ found that lymphocytes of patients with neuroblastoma had a cytotoxic effect in vitro against tumor cells from their own or other patients' neuroblastoma. In subsequent studies the Hellströms found the same effect in other tumor types.⁹⁰ Morton and associates⁹¹ showed that there was a rise in antibody titer after tumors were removed in bone and soft tissue sarcomas. Sir Michael Woodruff⁹² speculated that tumors may possess specific antigens in early disease and that these antigens decline as the disease progresses, possibly a way to explain variations in the growth rate in tumors.

Early work in immunotherapy included a report by Lloyd Old⁹³ and associates that injection of *Bacillus Calmette-Guérin* (BCG) produced a nonspecific stimulation of the immune system in mice. Morton and Eilber⁹⁴ tested the use of BCG in a clinical study involving 8 patients with malignant melanoma. Five of the 8 patients showed regression or disappearance of skin tumors. Kremenz and associates⁹⁵ irradiated cancer cells and injected them into 19 patients. In one of these patients with malignant melanoma, a complete regression of the tumor occurred and lasted until the patient's death four years later. Later, Kremenz and associates⁹⁶ developed a technique which combined cross-transplantation and cross-transfusion with plasma and white blood cells. They used the method in 56 patients with 9 different kinds of cancer including melanoma. In 3 patients with melanoma they observed regression which lasted 12, 46, and 51 months.

Murray⁹⁷ reported a study in which he inoculated a horse with tumor cells, collected a sample of gamma globulins from the horse's blood and injected it into patients with cancer. He reported an improvement when the injection was tolerated. More than 10 years after Murray's report, Coggin and associates⁹⁸ reported that humoral elements which retard or prevent the growth of tumor cells in vivo appeared to be immunoglobulin G-like. They seemed to precede the tumor's appearance and slowed the growth of tumor cells in animal models. In a series of immunological tests performed on patients with either benign breast disease or breast cancer who were part of a large interdisciplinary study in England, it was found that there was a positive correlation between the extent of metastatic breast cancer and the serum immunoglobulin levels, especially IgA and IgG.⁹⁹

However, Dr. David Weiss, while accepting that immunological mechanisms are important to the understanding of the neoplastic process, warned that one must not assume that the neoplastic cell is the only important element in the natural history of cancer. The relationship between the host, that is, the patient, the cancer, and the environmental circumstances must be taken into account. That there are dynamic interactions between the host, the cancer cells and the environment is true of malignant disease as well as infectious diseases can be seen by the “complex and shifting equilibria that characterizes the fluctuating course of illness, recovery, and immunity.”¹⁰⁰

Dr. Weiss warned that while the host-parasite model is valid and useful it is easy to distort or misplace emphasis. The role of the host has been the primary focus of work in this field which can overshadow the evidence that neoplastic cells can “counterattack.” He cited several pieces of evidence: Cancer cells can produce substances that are toxic to lymphoid tissue, are capable of degrading immunoglobulins enzymatically to produce “antibody fragments devoid of cytotoxic properties,” can shed cell membrane fragments into their environment, may block T-cell receptors and form a “barrier” around the tumor that can neutralize immune elements, can change their surface antigens, and have other means of escape from immunologic and other measures of control.

There has been some clinical research specifically directed toward spontaneous regression. Several clinicians have studied the effects of blood or blood plasma from patients in remission on patients with progressive disease. Sumner and Foraker in an article published in 1960 reported the effects of using blood from a patient who had experienced a spontaneous regression of malignant melanoma on another patient with the disease. “Within six weeks all the lesions disappeared or materially regressed. Three months later all had disappeared.”¹⁰¹ This study prompted others to try it. Teimourian and McCune reported a successful experiment in 1963.¹⁰² Ngu in 1967¹⁰³ reported a temporary regression from Burkitt’s lymphoma after plasma from patients who had uninterrupted remissions from Burkitt’s lymphoma for over 2 -and-a-half years was transfused into a patient with active disease. Fass and associates¹⁰⁴ however tried to repeat Ngu’s work without success. A similar technique was tried on a patient with clear-cell carcinoma of the kidney by Horn and Horn¹⁰⁵ with success. It should be noted that in both Ngu’s report and Fass and associates’, the plasma donors had been treated with cytotoxic drugs. In Sumner’s report the blood donor had had no cytotoxic treatment. The responses from the patients would indicate that the regression had some kind of immunological component.

Immunotherapeutic treatments for certain types of cancers, melanomas, renal carcinomas, and lymphomas, among others, have been used with some success. Research on the immunological mechanisms of cancer progression and regression continue. This avenue of research has increased our knowledge of the biology of cancer and that certainly will aid the search for future treatments.

Of course, immunological mechanisms are not the only ones that have been considered as possible causes of remission. Different authors have speculated on the phenomenon of spontaneous regression over the years and have proposed a number of possible biological mechanisms for remission. With the discovery of links between the brain and nervous system, the endocrine system and the immune system, the body’s primary information systems, perhaps the mechanisms of remission cannot be attributed to any one process but involve a wide range of interconnected processes, the scope of which we are just beginning to see. A look at the list of some of the biological mechanisms that have been proposed seems to indicate that these biological processes may follow similar pathways.

SUMMARY OF POSSIBLE BIOLOGICAL MECHANISMS OF REMISSION†

Proposed Mechanism	Possible Site of Action	Research/Author Reference§
Immunologic action/host resistance	Generalized, melanoma, lymphoma, neuroblastoma, hypernephroma	Gaylord & Clowes, Rohdenburg, McConnell, Everson & Cole, Boyd, Rosenberg, Old, Fass, Horn, Sumner, Ngu
Host-parasite relationship	Generalized	D. Weiss
Elimination of carcinogen	Bladder, melanoma	Everson & Cole, Nathanson
Surgical trauma	Generalized	Rohdenburg, McConnell, DeCourcy, Everson & Cole, Sindelar
Irradiation (other than tumor site)	Generalized	Everson & Cole
Infection/fever	Generalized, sarcomas	Rohdenburg, W. Coley, DeCourcy, Everson & Cole
Control of cell/DNA repair	Tumor site	Papac, Yunis, Firminger
Nephrectomy	Distant metastases	Fauvet et al., Everson & Cole, Schirmer
Endocrine/hormonal	Hypernephroma, melanoma, breast, ovary, testes	Everson & Cole, Boyd, Nathanson
Pigment metabolic	Melanoma	Nathanson
Intracellular (nonpigmentary)	Melanoma	Nathanson
Interference with nutrition/elimination of blood supply	Generalized, hypernephroma, solid tumors, neuroblastoma	Gaylord & Clowes, DeCourcy, Everson & Cole, Boyd, Folkman, Nathanson
Cell-mediated immunity	Generalized	Hellström & Hellström et al., Klein
Allergic reaction	Choriocarcinoma, melanoma	Everson & Cole
Wound infection/abscess	Neuroblastoma, stomach, colon	Rohdenburg, Coley, Everson & Cole
Cellular differentiation/fibrotic processes	Generalized, neuroblastoma, hypernephroma	Handley, McConnell, Evans, Bartley
Necrosis	Generalized	Gaylord & Clowes, Handley, Hodenpyl, McConnell, Rae, Everson & Cole
Ascitic fluid, immune plasma	Breast	MacKay, Hodenpyl, McConnell, DeCourcy, Krementz, Fass, Horn, Sumner, Ngu
Anti-angiogenesis	Generalized, solid tumors, melanoma	Folkman, Nathanson

† compiled by the authors.

§ partial list of references.

REMISSION: POSSIBLE BIOLOGICAL MARKERS

Thanks to advances in neurochemistry and genetic engineering we now seem to be at a point in history where the biological markers of remission may be detectable. Three examples are:

- Work at Sloan-Kettering in New York has built on the work of Dr. William Coley, who died in 1937. Coley was able to biologically induce remission in a significant percentage of patients using Mixed Bacterial Toxins and this led to the study of his techniques via an animal model which resulted in the isolation of Tumor Necrosis Factor [TNF].¹⁰⁶ This has now been cloned and is in clinical trials. (Much remains to be done with TNF in terms of isolation of the less toxic factors in this 13-component mixture.)
- Some of the more than 50 neurotransmitters now known may prove to be involved in remission, for example one neuropeptide called somatostatin has already been found to be depressed in patients with Alzheimer's, Parkinson's or multiple sclerosis (MS) and it has been found to be elevated in patients who are in remission from MS.¹⁰⁷ This is not to say it is the cause of the remission, but it does point the way to the fact that biological markers for remission are discoverable.

- In 1970, Sweden's T. O. Caspersson¹⁰⁸ developed a technique of staining cells during cell division by which he could detect 640 light and dark bands on the cell's chromosomes. He observed that if a person's chromosomes had specific bands missing or if a band had broken off and attached to another chromosome the person would often have a physical abnormality. However, there was limited resolution with the early staining techniques and the observed patterns were often very fuzzy.

Geneticist Dr. Jorge Yunis' elegant work built upon this procedure and through the use of an electron microscope almost 10,000 bands on the forty-six chromosomes in each cell can be detected, more than four times what was discernible in the earlier work. With his technique he has looked at cancer cells and has discovered that almost all cancers involve one or more chromosomal aberrations. He has said that these "fragile sites"¹⁰⁹ found on chromosomes may be involved in chromosomal defects that are found in connection with many kinds of cancer. He observed that hematopoietic cancers often involved translocation of chromosomal pieces while solid tumors such as cancer of the lung or colon usually involve missing sections. Dr. Yunis has found that if a patient's cancer cells have an upside-down section on the sixteenth largest chromosome then the chances of the patient's survival is excellent and the patient is likely to undergo complete remission.¹¹⁰ Interestingly, patients with this type of rearrangement are also three to four times more sensitive to chemotherapy.¹¹¹ This discovery has important implications for remission research.

REMISSION RESEARCH: BIOLOGICAL PROCESSES AND PRODUCTS

Although hormonal therapies were introduced in the 1940s and other biological treatments (such as Coley's toxins) had been used since the early 1900s, until the 1960s radiation along with surgery were the primary treatments for cancer. After World War II, the first chemotherapeutic agent, mustard gas, was tested for use as a cytotoxic agent in cancer treatment, and in the next 20 years many more chemicals were added to the list of drugs used for chemotherapy.

The observations of Dr. William Coley on remission of cancer associated with bacterial infections and fever and the subsequent development of Coley's toxins [see Appendix Four] and the work of Dr. Eugene Hodenpyl on the curative properties of ascitic fluid in cancer offer a glimpse into the process of scientific inquiry of the early 1900s, prior to the development of sophisticated techniques and tools. This pragmatic approach to the treatment of cancer based on observations of the association of biological processes and remission, the subsequent development and implementation of experimental models and, finally, initiation of "clinical trials" of the treatment provided the basis for the research procedures that have been used since that time.

Coley's Toxins and Infection

Toward the end of the last century, a physician named William Coley noted that some of his patients with cancer experienced remission when they contracted erysipelas, a bacterial infection caused by *Streptococcus pyogenes*.

Coley adopted the technique of deliberately infecting patients with this bacterium to induce remission, but he found that the infection wasn't that easy to induce. While he did achieve some dramatic results when the induction was successful, the problems with the live bacteria led him to try killing the bacteria with heat and adding another bacterium, *Bacillus prodigiosus* (now called *Serratia marcescens*), to the *Streptococcus pyogenes*. This combination of heat-killed "Strep" and Bacillus became known as Coley's toxins. He succeeded in a significant percentage of cases, particularly cases of sarcoma, though his approach was eclipsed when first radiation and then chemotherapy emerged as treatments for cancer.

The Remission Project's survey of the literature found a significant number of cases which also correlate remission with the incidence of infections such as smallpox, pneumonia, malaria and tuberculosis. [see Appendix Four] The common factor in all these infections is high fever, usually 104 to 105 degrees F. for several days (3 to 5 days). It should be noted that these infections do not always produce fevers that high or for that long. Coley's toxins do produce violent febrile reactions which do not usually last more than 24 to 48 hours. However, it would seem from the data that a temperature of at least 104 degrees main-

tained for from 48 to 96 hours is more likely to produce the remission than lower temperatures for shorter duration. This suggests a line of research that could be actively pursued to unravel the mechanisms involved in spontaneous remission.

The Cytolytic Effect of Ascitic Fluid

In 1910, Dr. Eugene Hodenpyl¹¹² observed the regression of multiple metastases in the neck, breast and abdomen and liver from breast carcinoma which he associated with “excessive chyloform ascites” in the abdominal cavity. Four years after the first operation, “with the exception of scars and decreasing emaciation, and extreme chyloform ascites, requiring frequent tapping there is now no indication of the original disorder.”¹¹³ Dr. Hodenpyl removed ascitic fluid from the woman and injected it into mice that had cancerous growths. He noticed either necrosis of the growths, diminution in size of the tumors, or complete disappearance. He then injected the ascitic fluid into human beings suffering with cancer, either into the tumors or near the tumors or in large quantities into the veins. There was a temporary redness, tenderness, and swelling, then a softening and necrosis of the tumor tissue which was absorbed or discharged externally, and the formation of connective tissue. In all 47 cases in which this technique was used the tumors either grew smaller or, in some cases, disappeared entirely. No other tissue reacted to the injections and no systemic effects were noted even after large intravenous infusions.

Plasma Transfusion

More recently, based in theory at least upon the observations of Hodenpyl on ascitic fluids, researchers have performed some preliminary experiments on the use of plasma from patients who have experienced remission in other patients with progressive disease.

There are indications from several research groups that experiments involving the removal of plasma from patients in remission from certain kinds of cancer have improved the condition of other patients with the same kind of cancer. This work continues internationally. Attempts have been made to replicate some of this work by Fass and Herberman at the Pittsburgh Cancer Institute, though without the success reported by others. Drs. Sumner and Foraker¹¹⁴ reported early work with “immune” plasma and malignant melanoma in the 1960s. Later work in the use of plasma was done in the early 1970s by Drs. L. Horn and Dr. H. L. Horn¹¹⁵ and Kremenz et al.¹¹⁶ Observations in the early 1900s about the curative effect of ascitic fluid on tumors implies that fluids other than plasma may have immune properties.

Endotoxins

Work on the use of endotoxin is the result of early work of William Coley and the work at Memorial Sloan-Kettering where the isolation of tumor necrosis factor was performed.¹¹⁷ It is believed that endotoxins cause certain cells in the body to secrete tumor necrosis factor which destroys tumors. Endotoxins are composed of a long chain of sugars (a polysaccharide) and a fat molecule (lipid A). They are produced by many bacteria and are responsible for the chills and fever that seem to go along with severe bacterial infections. They also appear to be responsible for enhancing immune response to bacteria and viral infections and cancer. When endotoxin is injected into animals bearing tumors the tumors regress in a percentage of the animals. Work is now underway to isolate a substance from endotoxin that has less of the toxic side-effects.

Ribi Pharmaceutical Company has specialized in working with a cellular extract (MPL) that may be similar to what is invoked by the Coley's toxins. This work by Ribi has isolated a substance that is less toxic and acts as a central stimulator of the immune system's own production of anti-tumor agents. In human clinical trials vaccine-like substance containing melanoma cell lysates produced remissions of melanoma in 5 of 17 patients.¹¹⁸

Angiogenesis

Research has been directed toward understanding the mechanisms of angiogenesis and gene expression in an attempt to understand how disease processes occur and perhaps find ways to circumvent or change these processes.

In mature adults angiogenesis (the process whereby new blood vessels are formed) is usually limited to reproduction or wound healing. It has been observed that the occurrence of angiogenesis at almost any other time is associated with a pathological process and has been associated with many life-threatening diseases, diseases such as atherosclerosis, arthritis and cancer.

Mechanisms reported to be associated with spontaneous regression of tumors are surgical trauma, necrosis, interference with nutrition of the tumor, or elimination of the blood supply. All of these may be related to the same process, that is, the elimination of the network of blood vessels that supply the tumor with nutrients. It has been postulated that tumors have mechanisms for stimulating the growth of blood vessels to supply themselves with nutrients from the rest of the system.

Work by Judah Folkman¹¹⁹ at Harvard and other researchers throughout the world has focused on understanding the process of angiogenesis and the development of substances that have anti-angiogenic properties. Tumor necrosis factor (alpha TNF), alpha interferon (alpha INF) and transforming growth factor β (TGF- β) have been reported to suppress the development of blood vessels. Though not yet tested in humans, human platelet factor 4 (PF4) has been shown to inhibit angiogenesis in animal models.¹²⁰

A recent survey of the work in this area was published as a bibliography by the National Cancer Institute. Several classes of compounds have exhibited anti-angiogenic properties including steroids, polysaccharides, retinoids, and peptides. Animal work has been published which shows the effects of some of these products. However, there are potential dangers from them at present: Specifically, hemorrhaging has occurred in some of the animal trials. Some of these products are either in animal trials or in human clinical trials, among them an analogue of a naturally secreted antibiotic of *Aspergillus fumigatus* frese-
nius, fumagillin (AGM 1470),¹²¹ a polysaccharide which is in clinical trials with AIDS-related Kaposi's sarcoma,¹²² retinoic acid analogues,¹²³ shark cartilage extracts,¹²⁴ and steroids such as tetrahydrocorti-
sol.¹²⁵ These compounds, among others, have enormous potential anti-cancer applications.

Oncogenes

At least 85 oncogenes, growth-factor and cell-specific genes have been detected that have some function in the neoplastic process.¹²⁶ It has been suggested that the beginning of the cancer process starts with the genes. When certain genes, the oncogenes, are altered by mutation they can promote abnormal cell proliferation. This is only one step in a series of complex steps that causes cancer. Another type of gene has been discovered that acts to suppress proliferation. When these growth suppressor genes are lost, another restraint on proliferative growth is lost.¹²⁷

The suppression of oncogene expression, of host- or tumor-growth factors, or the loss of oncogenes may stimulate spontaneous regression or tumor dormancy. Natural processes or chemical agents may trigger these changes. Perhaps looking for oncogenetic abnormalities or alterations in oncogene expression in patients who show spontaneous regression may provide clues to the mechanisms of remission. Also, work is underway looking for ways of "turning off" these cancer stimulating oncogenes, "turning on" growth suppressor genes and reversing the neoplastic process. This work is at a very preliminary stage at this point but holds promise for understanding the neoplastic and other disease processes.

Organ Transplants and Immunosuppression

An area of research that holds promise for understanding how immune processes influence the development, progression and regression of lymphoproliferative diseases and other forms of cancer has developed from observations of transplant patients.¹²⁸

Immune suppressant drugs are given to patients who undergo organ transplants in order to prevent the rejection of the transplanted organ. It has been observed that under the influence of these drugs a small number of the patients develop either lymphoproliferative disease or Kaposi's sarcoma. When the immune suppressant drugs are discontinued, in some cases the lymphoproliferative disease or Kaposi's sarcoma spontaneously resolves. Several reports of this phenomenon have appeared in the medical literature. By studying the immunological markers of these patients during both the development and regression stages, important information about the possible immune mechanisms related to remission can be obtained.

Advances in Immunotherapy

In 1968, when Dr. Steven Rosenberg was a surgical resident he observed a case of spontaneous regression in a patient with liver metastases from a gastric carcinoma.¹²⁹ The patient, a 63-year-old man, had returned to the hospital for a gallbladder surgery 12 years after he had been given a terminal diagnosis. Dr. Rosenberg, in search for an explanation for this remarkable occurrence, re-examined the surgical report, the pathology slides, and the hospital chart. The original surgeon's report indicated that a large tumor was found in the man's stomach, 3 smaller tumors were found on the liver, and the lymph nodes were hardened. The largest tumor and two-thirds of the stomach were removed but the other tumors were left because it was felt that removal would have little benefit. The pathology report confirmed the seriousness of the disease and noted that there was a large number of lymphocytes and eosinophils in the tumor area. Examination of the hospital records indicated that a serious stomach infection developed after the operation which required re-opening of the wound 10 days later. He was expected to die within months and yet 12 years later he was well. Upon surgery for removal of the gallbladder, Dr. Rosenberg found no evidence of cancer after a thorough examination of the abdominal cavity.

If we could somehow understand how this had happened, if we could somehow understand the mechanism, if we could somehow duplicate the mechanism in other patients. . .
Something began to burn in me, something that has never gone out.¹³⁰

He reasoned that this patient's immune system had somehow destroyed the cancer. This began his sustained research efforts to understand how immune processes influence the development of cancer and to find immunotherapeutic approaches to the treatment of cancer. First he attempted unsuccessfully to transfuse another patient with the blood of the spontaneous regression patient.

After many years of trial and error, he discovered that he could take a patient's own immune cells from their tumors, teach them to fight cancer by treating them with cytokines like interleukin-2 (IL-2) or with primitive lymphocytes called lymphokine activated (LAK) cells, put them back in the patient and cause some cancer regression. (LAK cells are "primitive" lymphocytes, lymphocytes that can attack cancer cells and other cells nonspecifically without having to recognize a specific antigen.) He called the procedure adoptive immunotherapy or cell-transfer therapy. Using a combination of IL-2 and LAK cells he achieved objective regression in about 10% of the patients with melanoma and kidney tumors. Results of that study were published in 1985.¹³¹

Encouraged by their work with LAK cells, Rosenberg and colleagues then searched for other cells that might be more potent against cancer. They found that tumor infiltrating lymphocytes (TIL) were 50 to 100 times more effective than LAK cells in causing regression. In a clinical trial with malignant melanoma patients who had received a single dose of cyclophosphamide (an immunosuppressive drug) using TILs and IL-2, he observed regression of melanoma in 9 of 15 patients who had not been previously treated with IL-2 and in 2 of 5 patients who had been treated unsuccessfully with IL-2.¹³² It appears that TILs work by accumulating around cancer sites. They destroy tumor cells not only by direct contact but also by producing cytokines (tumor necrosis factor is a cytokine) that are capable of mediating tumor cell killing.

In an effort to improve the therapy with TILs and IL-2, Dr. Rosenberg has collaborated with others to make small changes in the gene structure of TILs. These genetically engineered cells have a two-fold purpose. First, it is believed that they will enhance the immunotherapeutic treatment and, secondly, they provide a genetic marker to enable the researchers to study in detail the mechanisms of action and distribution of these "designer" TILs against tumors. In a paper published in 1990, Dr. Rosenberg and colleagues used this method on 5 patients with progressive melanoma in whom other treatments had proven ineffective. This was the first time foreign genes had been introduced into humans. Three of the 5 patients showed antitumor effects with complete regression of cutaneous, mucosal and lung metastases in 1 patient. The study also demonstrated that the gene-modified TIL can survive for several months in the blood and at the tumor sites.¹³³ This process is far from perfect; it is complex, expensive and has severe side-effects. However, through the efforts of Rosenberg and others, immunotherapeutic techniques have now been added to surgery, radiation, and chemotherapy as approaches to the treatment of cancer.

Metaphors of the mind's influence include likening it to the weak force in physics, the trim tab in aeronautics, and the catalyst in chemistry. In physics, the weak force is needed to complete the symmetry of nature; it is not strong but is vital at the subtle level. In aeronautics, the trim tab on an aeroplane is that tiny carefully shaped fin on a plane that plays a dominant role in altering the direction of the whole structure. In chemistry, the catalyst is that substance that lowers the energy required for a reaction, but remains itself unchanged at the end of the sequence.

1992: Brendan O'Regan

REMISSION AND SURVIVAL: WHAT IS THE ROLE OF THE MIND?

The Placebo Effect

Dr. Robert Ader has said, "If a physician gives you a pill that contains no ingredients known to influence your rash, your cold symptoms, or your pain, for example, but you experience relief from whatever ails you, that's the 'placebo effect.'"¹³⁴ This placebo effect has been one of the most constant indications that a wide variety of conditions can be positively affected by an as-yet-unknown internal system in virtually every person. An extensive survey of the medical and research literature on the placebo effect in medicine reveals that the spectrum of self-repair is at least partially unexplored. Among those conditions that have proven responsive to placebo treatment are angina pectoris, cancer, rheumatoid arthritis, warts, asthma, ulcers, migraine headaches, allergies, multiple sclerosis, diabetes, and psychiatric disorders.

It is now clear that these conditions are not limited to those that would normally be classified as "psychosomatic" in origin. This fact is important because it has often been assumed that if a disease is psychological in origin, then it can be expected that a shift in the psychological status of the patient can alter it. Though such cases are in the placebo literature, there are also many cases where the effects are directly physical even though they are somehow mediated by the psychological level, acting as a biological response modifier.

Examples include:

- Dr. Philip West¹³⁵ reported some years ago on the case of a man with severe cancer who begged to be given a dose of an experimental drug called Krebiozen, which was being touted as a "wonder drug." After one dose of this drug, the patient's tumor masses "melted like snowballs on a hot stove." The patient no longer needed an oxygen mask to breathe and even resumed piloting his own plane. When the man later read further reports that the drug was worthless, his cancer immediately began spreading again and he required hospitalization. He died a few days later.
- In 1961 Dr. Henry Beecher¹³⁶ reported on a study in which he divided patients scheduled for heart surgery for treatment of angina pectoris into two groups. One group had the full surgery. The other was cut open and simply sewn back up. Both groups were told they had the full operation. Follow-up studies indicated that all the patients fared equally well and so it was shown that surgery for angina pectoris was a placebo.
- A case in the World Journal of Surgery in 1983¹³⁷ reporting a placebo-controlled trial of a chemotherapy agent revealed that 30% of the control group receiving a placebo lost all their hair.
- Dr. Robert Ader has studied the placebo effect in mice with immunological disease. In his experiments using classical conditioning techniques one group of mice received cyclophosphamide (an immunosuppressive drug) paired with saccharin. A second group received half the drug dosage again paired with the saccharin. A third group also received half the dosage but the placebo was given at a different time. The results showed that the first group survived longest and the second group survived significantly longer than the third. The implications of these results indicate that the second group of mice learned

to associate the placebo with the immunosuppressant and that the saccharin was able to produce some of the drug's effects by itself.¹³⁸

Based on these experiments he has suggested that drug-placebo studies with humans should be conducted. If these studies are fruitful, and preliminary information from one patient indicates that this is so,¹³⁹ there could be many benefits including lowered drug doses, particularly with chemotherapeutic agents that have toxic side-effects.

Clinicians and researchers agree that expectation and belief are important mediators of the placebo effect. In 1973, Dr. Jerome Frank, professor emeritus of psychiatry at Johns Hopkins at the time, tells the story of a German doctor who used the "healing power of expectant faith" in his placebo experiment with three very ill bedridden women:

One was near death with cancer of the uterus, one had a severely inflamed gall bladder and gall stones, and a third was having a very difficult time recovering from abdominal surgery. The doctor had tried everything that conventional medicine had to offer, so he decided to try faith healing. First, he asked a local faith healer who claimed to heal at a distance to try. Nothing happened to the three women. Then he told the women that the faith healer would perform the healing on a specific day. After that day, the three women began to improve. The woman with gallbladder problems lost all her symptoms with no recurrence for several years, the woman who had abdominal surgery for an inflamed pancreas began to recover, and although the woman with uterine cancer eventually died, she lived the last three months of her life without the pain, weakness, and ascites that had kept her bedridden.¹⁴⁰

As result of these and other studies, more thought has been focused on the importance of the natural self-repair capabilities possessed by each individual to varying degrees. The healing of wounds is the most commonly known form of self-healing. However, more and more, the evidence is beginning to show that profound and "system-wide" self-repair mechanisms may exist. If it is possible to imagine that there is a spectrum of responses that can be brought about by each individual's natural self-repair mechanisms, then the placebo effect is an example of its operations at the low end of the scale and remission is its effect at the high end of the scale.

An interesting thought from H. M. Spiro: "The placebo stands at the center of the conflict between science and intuition, reminding physicians that science alone may not be sufficient for medical practice."¹⁴¹

Psychoneuroimmunology

One area of inquiry that shows great promise as a rigorous scientific approach to discovering how mind states might affect healing is the emerging science of psychoneuroimmunology [PNI]. PNI has uncovered links between the "mind" and other major information systems of the body, systems which until recently were firmly believed to be separate; the neuroendocrine system, the brain and nervous system and the immune system. These systems have some functional similarities: They send and receive information both from within the organism and from outside, they learn from what they receive, and they remember what they have learned. Research in PNI is attempting to uncover the mechanisms that mediate psychological and psychosocial influences on health, healing and immunity. Since an immunological mechanism is postulated as the primary biological mechanism involved in remission, and there are now proven links between the nervous, neuroendocrine and immune systems, it is interesting to speculate on their interplay and how that might influence remission.

PNI research has discovered that nerves permeate the lymphoid organs, that peptides from the brain are found in the digestive tract, that states of mind like grief, stress, and joy can alter immune response and that the immune system can affect the brain and states of mind. While there is only indirect evidence at present that changes observed in immune measures have a correlation with disease onset or outcome, the research does show conclusively that states of mind can affect how the body's defense system functions.

Perhaps in the future, psychoneuroimmunological research will be able to help elucidate the biological mechanisms of action of the placebo effect, hypnosis and trance, meditation and prayer, and explain how emotions like joy, love, fear and grief can affect healing.

Hypnosis

Medical journals contain many stories of healing associated with hypnosis and other dissociative states. Hypnosis has been reported to speed the healing of burns, cause warts to disappear, cure asthma and decrease blood loss in surgical procedures.

The disappearance of warts through the use of hypnosis has been reported by many authors. That warts, a viral infection, can be cured through the use of a mental technique prompted noted physician and writer Lewis Thomas to propose a national study of the effect of mental practices on warts.¹⁴² Perhaps hypnosis can affect the immune system which is responsible for defending the body against viral attack.

Hypnosis was used as anesthesia prior to the introduction of ether and an early report of hypnotic anesthesia gives an intriguing glimpse into a possible role of the mind in remission.

The report entitled "An 1846 Report of Tumor Remission Associated with Hypnosis" describes the case of a woman diagnosed with breast cancer who was hypnotized by La Roy Sunderland (1804-1885), a clergyman who developed a theory and method of hypnosis which he termed "pathetism." Mr. Sunderland worked with the woman for several days and then accompanied her to the operating room, where he used hypnosis as anesthesia prior to operation. The surgeons to their surprise could not find the tumor.¹⁴³

Altered States

Altered states such as ritual trance, prayer, meditation and other spiritual practices such as yoga, zen and Buddhist training have also been reported to enhance healing.

Dr. Ainslie Meares has reported several cases of remission of various types of cancer using a technique of meditation he calls "atavistic regression." He theorized in one of his papers that "Hypnosis and meditation are slightly different manifestations of the same basic process. I have shown that atavistic regression is the basic mechanism of hypnosis."¹⁴⁴

Miraculous Healings

The reports of miraculous healings, such as those reported at Lourdes, show the extent to which faith and prayer can affect healing. These reports are very well documented and rigorously reviewed by the International Medical Commission of Lourdes. To date there have been 65 cures accepted as miraculous by the church. There are very specific requirements for a healing at Lourdes to be submitted to the commission for evaluation:

First, the cure itself. It must be sudden and unforeseen, and without convalescence, complete, lasting for 3 or 4 years at the minimum, before it is admitted. Then, the disease itself. It must be serious, a danger to life; organic and not functional, based on a definite disease. For example, loss of speech, which was not an aphasia following a cerebral lesion, would not have much chance of being upheld; objective, proved by tests, X-rays, biopsies, etc. which must be produced. Finally, modes of treatment which have, or could have, been used. Tuberculosis, for example, which was one common amongst the cures, has practically disappeared completely today, due to effective and specific modern treatment. (Dr. Théodore Manganapan, *Cures and Miracles in Lourdes*, 1984)

In the remission literature, Fauvet et al.¹⁴⁵ in 1960 reported the case of Sister Gertrude whose recovery from pancreatic cancer was attributed to the prayers of the Mother Superior of her order. Fauvet commented that "it is understandable that in certain of these instances a miracle cure was under discussion. It must however answer to the four criteria which we believe are indispensable: sudden recovery, total, definitive, and inexplicable." While these miracles appear to show a different course than cases of remission, they are sudden and complete, whereas remission can be gradual, taking place over weeks

or months. Also, remissions can be temporary, while the miraculous healings of Lourdes are cures, that is the disease doesn't return, although there is one report of a miraculous cure of Budd-Chiari syndrome where the patient subsequently died from a recurrence of the disease.

Group Support

A landmark piece of research found that breast cancer patients who participated in a support group survived twice as long on the average than those who did not. It is interesting to note that the only kind of psychological technique they used in the support group was self-hypnosis for pain.

Dr. David Spiegel and colleagues¹⁴⁶ studied the effect of psychosocial intervention on time of survival of 86 patients with metastatic breast cancer. The one-year intervention consisted of weekly support group therapy with self-hypnosis for pain. At follow-up ten years later, only 3 patients were alive and these patients had participated in the one-year intervention. The most significant finding is that the patients who had participated in the support group therapy survived on the average 36.6 months from time of randomization and onset of intervention as compared with the control group who survived an average of 18.9 months.

Other Psychospiritual Factors

Although most of the body of knowledge regarding the role of the mind in healing has been accumulated from studies of long-term survival, it is argued by some that the mechanisms that affect remission and survival may be, if not the same, at least similar. Dr. Ikemi and his associates have included in their definition of spontaneous remission the "long survival of the host body."¹⁴⁷ Whether the psychospiritual correlates of survival can also be associated with remission remains unknown until there is more systematic research on remission. That the mind plays a role in remission and survival is now acknowledged by many in the medical community, but what that role is and how much of a mediating influence psychospiritual factors have in the remission and survival process is unknown.

Five studies, 4 with cancer patients and 1 with AIDS patients, in which psychospiritual characteristics of long survivors or spontaneous remitters were evaluated, seem to support the hypothesis that there is a similarity in the psychospiritual correlates of remission and long survival:

- The work of Steven Greer, though it has been the subject of some controversy, found that mental survival provides another look at a possible link between remission and psychological states of mind.

Dr. Greer and associates¹⁴⁸ conducted a ten-year study of women who were admitted to hospital for breast biopsy in 1977. Psychological stress from mastectomy, depressive symptoms, marital, sexual and interpersonal adjustment was determined for each follow-up period. Five separate categories of psychological responses to diagnosis were found. These included denial, fighting spirit, stoic acceptance, anxious/depressed acceptance, and helpless/hopeless response. At five years after biopsy, those patients whose responses showed denial or fighting spirit (15/20, 75%) had a more favorable outcome than those patients who showed either stoic acceptance or helplessness/hopelessness (13/37, 35%). At ten-year follow-up, Greer and associates found a higher mortality but still found a better outcome for those who responded with fighting spirit or denial (11/20, 55%) than those who showed stoic acceptance or helplessness/hopelessness (8/37, 22%).

- In 1975, Dr. Yujiro Ikemi and associates reported 5 cases of spontaneous remission in which they noted the psychosocial factors associated with each case. The commonalities between cases were noted. Each person seemed "to have overcome cancer by accepting responsibility for resolving such a crisis for themselves."¹⁴⁹ A passionate religious faith was shared by 4 of the cases and all cases reported that they had left their outcome to fate or the will of God. Also, each person showed a dramatic change in outlook on life.

- In a study of 6 cases of spontaneous remission from advanced cancer, Drs. van Baalen, de Vries, and Gondrie¹⁵⁰ found that the group shared common psychosocial characteristics, changes in behavior, and relationship toward the environment. They all showed a relatively sudden change toward increased auto-

nomous behavior and also significant changes in their attitudes toward their illness, their treatment, their relationships with other people, their spiritual beliefs, and their environment. The authors concluded that the psychosocial factors involved in spontaneous remission are trust, challenge, commitment and control.

- Dr. Paul Roud¹⁵¹ interviewed 9 patients who had experienced extraordinary survival after a “terminal diagnosis” of cancer. The patients’ physicians were contacted and asked to confirm, or not, the exceptionality of these patients. To qualify, the physicians had to confirm that the probability of these patients’ survival was 25% or less. In all cases except 1, the probability of survival according to the physicians was less than 10%. Four of the 9 patients were given a less than 0.1% probability of survival. There was a great similarity in responses among the interviewees. Taking responsibility for illness onset, outcome, and quality of life, changes in interactional styles, the importance of close relationships and support, letting go of fear and worry, that is, attitudinal changes, more autonomous behavior, and a strong desire to live were the reasons given by the patients for their extraordinary survival.

- In a pilot study of long-term survivors with AIDS, Dr. George Solomon and associates¹⁵² found that the survivors had a number of psychosocial characteristics in common. The long-surviving people with AIDS perceived their physicians as partners in their treatment and did not act in either a defiant or passive mode when consulting with their physicians; long survivors accepted the diagnosis and took a personal responsibility for the disease, but did not perceive it as a death sentence, and felt they could influence the outcome; many felt they had unfinished business, unfulfilled goals, or activities they were looking forward to in the future; survivors had a sense of purpose and found new meaning as a result of the disease; they altered their lifestyles to accommodate the disease and engaged in some kind of physical fitness or exercise program; and several had a prior life-threatening illness or other serious life event that they had successfully overcome. In general, survivors were assertive and able to say “no,” were able to nurture themselves by withdrawing from stressful involvements if necessary, were able to communicate openly about their needs, and were actively involved with others with the disease.

Most of the reports that correlate psychological and spiritual processes and remission are anecdotal with few case reports that include both psychosocial factors and physical diagnostic information appearing in the literature. As a result, there is a tendency on the part of the medical community to overlook reports of remission associated with psychospiritual factors. If there are common psychospiritual responses to a life-threatening disease that can successfully cause the disappearance or arrest of a neoplastic process or delay a fatal outcome, they should be discovered and the information incorporated into a multimodal prevention and treatment program. Rather than discount such reports because of the inadequacy of their diagnostic information, one should ask, are there cases of remission that are strongly linked to psychological and spiritual changes, and, if so, how might they best be studied?

PSYCHOSPIRITUAL CORRELATES OF REMISSION †

A summary of the reported psychospiritual correlates of remission that have been referenced in *Spontaneous Remission—An Annotated Bibliography* is presented here in chart form. Some of these are external modifiers, that is, therapeutic techniques, and others are internal changes. Many of these categories have characteristics in common and their separation in this chart is for organizational purposes only.

Psychospiritual Mechanisms	References§
Group support	D. Spiegel et al., H. Morgenstern, M. deVries et al., P. Roud, S. Levy et al., G. F. Solomon et al.
Hypnosis/suggestion	M. A. Gravitz, B. W. Newton, D. Spiegel et al., O. S. Surman et
Meditation	A. Meares, J. Kent et al.
Relaxation techniques	O. C. Simonton, S. Matthews-Simonton et al., J. Kent et al.
Mental imagery	O. C. Simonton, S. Matthews-Simonton et al., B. W. Newton
Psychotherapy/psychoanalysis	LeShan & Gassmann, Bowers & Weinstock, H. A. Selvey, B. W.
Behavioral therapy	R. Grossarth-Maticcek & H. Eysenck
Group therapy	H. Morgenstern et al., D. Spiegel et al., B. Newton
Miraculous spiritual phenomena	Lourdes Medical Commission, J. Garner, S. J. Dowling
Prayer/spiritual belief	S. L. Shapiro, G. Booth, J. Garner, S. J. Dowling, Y. Ikemi et al.,
Religious/spiritual conversion	Y. Ikemi et al, Bowers & Weinstock
Autonomous behavior/increased autonomy	M. de Vries et al., M. Wirsching et al., C. Weinstock, P. Roud, G. F. Solomon
Faith/positive outcome expectancy	M. de Vries et al., P. Roud, G.F. Solomon et al.
Fighting spirit	S. Greer et al., M. de Vries et al., G. F. Solomon et al.
Denial	S. Greer et al., M. de Vries et al.
Lifestyle/attitude/behavioral (changes)	G. Booth, S. Nakagawa et al., M. de Vries et al., R.T.D. Oliver, P. Roud, H. D. Foster, T. G. Hislop, Y. Ikemi et al., G. F. Solomon, J. Kent et al.
Social relationships/interpersonal relationship changes/family support	S. Nakagawa et al., M. de Vries et al., P. Roud, B. J. Kennedy et al., G. Booth, G. F. Solomon et al.
Positive emotions/acceptance of negative emotions	S. M. Levy et al., C. Weinstock, G. F. Solomon et al., J. Kent et al., B. A. Stoll
Environmental/social awareness/altuistic	M. de Vries et al., P. Roud, G. F. Solomon et al.
Expression of needs/demands/self-nurturing	M de Vries et al., M. Wirsching, G. F. Solomon et al.
Sense of control/internal locus of control	P. Roud, C. Weinstock, G. F. Solomon et al.
Desire/will to live	P. Roud, M. de Vries et al., Y. Ikemi et al., C. Weinstock, G.
Increased or altered sensory perception	M. de Vries et al., Y. Ikemi et al.
Taking responsibility for the illness	Simonton et al., C. Weinstock, P. Roud, G. F. Solomon et al.
Sense of purpose	G. F. Solomon et al., C. Weinstock
Placebo effect	B. Klopfer, C. Weinstock
Diet/exercise	G. F. Solomon et al.

† Chart compiled by the author.

§ A partial list only.

SPONTANEOUS REMISSION: IMPLICATIONS FOR RESEARCH

A systematic study of spontaneous remission is clearly needed. Studies of long-term survivors of normally fatal diseases with a view to assessing unusual biological or psychobiological features have never been done and it seems likely that a wealth of data would naturally emerge from such work. Studies of remission subjects, who display unique mechanisms of self-repair or disease reversal, may contribute significantly to the fundamental groundwork for a scientific understanding of the power of the immune and other biological systems—perhaps aided by the mind—to challenge and sometimes reverse what are normally considered to be fatal diseases.

There is, for instance, rising interest in studying the blood and tissue of patients in remission from various diseases as a means of detecting clues about how to stimulate remission. With the advent of genetic screening techniques and other sophisticated tools for cloning rare biological substances, medical science may now be in a unique position to take advantage of cases of remission. One could even argue that remission research could comprise an important avenue for the future development in the pharmaceutical and genetic engineering industries.

In addition, the field of psychoneuroimmunology has begun to allow us to monitor a possible role for mind-body relationships in remission in ways never before possible. Preliminary data indicate that there are commonalities between remitters. Interviews with remitters and long-term survivors could provide answers to questions about the common psychological and psychosocial denominators among these groups: What do people in remission have to tell us about their healing process? Do they hold certain kinds of beliefs or attitudes? Did they practice any discipline or health practice in common? What are their spiritual beliefs? Also, it is increasingly accepted today that the positive emotions (one of which is the belief that one can get well) stimulate the immune system and can be important factors in overcoming disease.

SPONTANEOUS REMISSION: IMPLICATIONS FOR PATIENT AND HEALTH CARE

Data from remission research data could have an important impact on patient care, helping to create the patient support-environment most conducive to remission, healing and quality of life. Increased awareness of and dialogue about the dynamics of remission could also inform the medical profession's approach to a very sensitive issue in medical care today—the issue of how and how much the healing environment and the patients' beliefs about their prognosis interact with one another.

On the one hand, there are those who claim that a positive mental attitude can affect survival and outcome and there are studies (Notes 147-152) that support this point of view. On the other hand, there are those who feel that “biology is destiny” and that to suggest attitude can affect outcome encourages false hope. Admittedly, the issue is a complex one without simple answers.

For example, it has been suggested by some that a “terminal diagnosis” can act like a self-fulfilling prophecy, and there are cases reported in the literature¹⁵³ in which withholding the diagnosis of cancer may have been what enhanced the patient's survival. While it is not suggested that patients should not be told their diagnosis, it can be argued that telling patients what their “chances” are could cause despair in some patients. In others, of course, the information may be just what is needed for the patient to rally his or her resources. In either case, instead of worrying so much about false hope, perhaps we should give equal concern to the dangers of creating unnecessary despair. Clearly, solid data on remission might give the concerned physician support for providing “ethical hope,” which is again being recognized as an important biological response modifier, helping to mobilize patients' will to live together with other intangibles that somehow affect recovery and the return to health.

If it proves possible to predict that there are those who are more “remission prone” and therefore present a lower risk for insurance and presumably consume less health care than others, this could have important cost reduction implications for the health-care system as a whole. With the estimate that medical care costs in 1992 are 12.3% of the Gross Domestic Product of the United States¹⁵⁴, it would be of great benefit to find ways to cut medical costs and redistribute the savings to research into disease prevention. Conversely if it becomes possible to identify a high-risk population, this could become an important factor in patient care and also for certain aspects of both health-care insurance and cost containment.

Near the end of the thirteenth century a zealous young priest of the order of Servites fell ill with a painful cancer of the foot. He bore his trial without a murmur and, when it was decided that amputation should be performed, spent the night preceding the operation in prayer before his crucifix. He then sank into a light slumber from which he awoke completely cured—to the amazement of the doctors who could no longer detect any trace of the disease. The holy man lived to the age of eighty and died in the odor of sanctity. He became known as St. Peregrinus, the patron saint of cancer.

S. L. Shapiro, Eye, Ear, Nose, Throat Monthly; 46(10): 1306-1310; 1967.

SPONTANEOUS REMISSION: CONCLUSION

Why do some people experience spontaneous remission of normally fatal diseases? What is unique about them, and what do they have in common? Are there genetic or chromosomal patterns that predispose one person to remission and/or another to progression? Is there a genetic composition or combination that initiates self-repair mechanisms? Are there some people whose healing systems are better at recognizing “not self” or, to say it another way, have a “better” ability to recognize and, hence, maintain the integrity of “self”? Can the mind mediate in the disease process to aid in remission? Does strong religious belief, faith or prayer, as the Lourdes cures seem to imply, provide some extra impetus that initiates some mechanisms of natural self-repair?

The more remission is recognized as legitimate and the more it is understood, the more likely it is we can understand how to stimulate natural self-repair capacities that exist in everyone to some degree. Innovative approaches to research in the past and present can lead to new therapies for people with life-threatening diseases in the future. Some of the new research avenues have been enumerated and many more exist that have not been discussed.

There are no medical journals devoted to the study of spontaneous remission. There is no National Remission Registry. There is no systematic approach to the study of cases of spontaneous remission or to possible mechanisms of remission. There is no course offered in medical schools devoted to the study of this phenomenon. It isn't even known how often spontaneous remission occurs, in what kinds of people, and in what diseases.

We hope that this volume will be the beginning of a systematic study of spontaneous remission, and will promote it as a viable research area. We hope that this book will encourage and stimulate physicians to publish their cases of spontaneous remission in refereed medical journals so that an epidemiology of remission can emerge. We hope that physicians and lay people will use this book as a reference and that the material contained herein will be a source of information and inspiration.

Sausalito, California
April 1993

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