Cancer begins and ends with people. In the midst of scientific abstractions, it is easy to forget this one basic fact. Doctors treat diseases but they also treat people and it is this precondition of this dual existence that drives them in two directions at once

- June Goodfield

Diseases desperate grown
By desperate appliance are relieved
Or not at all.

- William Shakespeare
What is it that I am fighting?

Why am I fighting it?

When will we know if we have won or lost?

- my patient, G.B.
Edwin Smith Papyrus, 2500 BC
Case 45: “A bulging mass in the breast, as dense as the hemat fruit”

A bone tumor found in a mummy from the 5th dynasty (2000 BC)
GALEN AND VESALIUS

Scultetus mastectomy
1595-1645

BLACK BILE AND HUMORAL THEORIES
A DISEASE OF CELLS:

1860 - 1960
VIRCHOW: A DISEASE OF CELL DIVISION

BOVERI: CHROMOSOMAL CHAOS
1860-1910 The age of surgery and radical surgery
"The patient was a young lady whom I was very loath to disfigure."

100 years later... the complete follow up of radical versus non radical breast surgery.

The limits of radical breast surgery.
Willy Meyer: “If a systemic therapy could be applied after the operation.”

Paul Ehrlich

Mustard Gas at Bari

<table>
<thead>
<tr>
<th>Day</th>
<th>Leucocytes</th>
<th>Polys</th>
<th>Lymphocytes</th>
<th>Turck Cells</th>
<th>Mononuclear and Transitional</th>
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Yellow Gas poisoning.. Krumbhaar & Krumbhaar

1910-1940: CHEMOTHERAPY INVENTED
Sidney Farber, doctor of the dead
(1903 – 1973)

1948-1950: Antifolates and temporary remissions

Watching His Dream Continue to Grow, 1972. Looking out from his office windows on the top floor of the Jimmy Fund Building, Dr. Sidney Farber could watch construction progress on the Charles A. Dana Cancer Center across the street. The building represented the embodiment of Farber’s dream for a comprehensive cancer facility. (Boston Herald.)
Temporary Remissions in Acute Leukemia in Children Produced by Folic Acid Antagonist . . . Aminopterin

Sidney Farber, M.D., et al.*
Emil Frei and Emil Freireich, NCI, 1950s

1955-1965: CHILDHOOD LEUKEMIA CURES AT THE NCI

Henry Kaplan, Stanford 1960s
Mary Lasker: “the fairy godmother of biomedical research”
Mr. Nixon:
You can cure cancer.
Expansion of the NCI budget

Effects on cancer mortality
A DISEASE OF GENES

1970 - 1990
ALTERATIONS IN GROWTH CONTROLLING GENES CAUSE CANCER

“A distorted version of our normal selves”
From sweeping to smoking: prevention and epidemiology
A DISEASE OF GENOMES

1990 - 2010
ALTERATIONS IN GROWTH CONTROLLING GENES CAUSE CANCER

HOW MANY?

HOW COMMON?
From ONE Gene to MANY Genes

Normal cell → Hyperproliferation → Early adenoma → Intermediate adenoma → Late adenoma → Carcinoma → Metastasis

APC gene mutation → K-ras mutation → DCC gene mutation → p53 mutation → Others
Hundreds of genes mutated in any individual cancer

(adapted from work by Vogelstein and others)
(adapted from work by Vogelstein and others)
Hundreds of genes mutated in any individual cancer

(adapted from work by Vogelstein and others)
WHOLE GENOMES = 4677

TOTAL MUTATIONS = 770,801

GENES MUTATED = 21,850

“DRIVER” GENES = 487

TARGETED GENES = 14
The age of targeted therapy

Acute Promyelocytic Leukemia
Chronic Myelogenous Leukemia

The four minute mile of cancer pharmacology

(adapted from work by Druker, Sawyers and others)
AN ORGANISMAL DISEASE

2010 - ??
ORGANISMAL: of, or pertaining to, an organism as whole, including its physiology, environment and interactions.
ORGANISMS:

Live by virtue of complex physiological pathways

Live within complex networks

Interact with complex environments
CANCER AS A “PATHWAY DISEASE”

MUTATION
↓
RAS
↓
CANCER

Yeang, McCormick and Levine, FASEB Journal, 2008

Friedman and Perrimon, Sci Signaling, submitted
THE LAST LAUGH OF LEUKEMIA

Mukherjee et al, unpublished

COMPLETED 40 exome SEQUENCES OF PATIENTS WITH MDA AND AML

BLOOD DEVELOPMENT

METABOLISM: IDH1 AND 2

METHYLATION: TET2 AND DNMT3A

IMMUNE MEDIATORS
Three shifts in paradigm: ONE

Iterative versus transformative

Survival $\uparrow$

Time $\rightarrow$

VS
Three shifts in paradigm: TWO

OLD: Try and Try again

Trial 1 → Trial 2 → Trial 3 → Trial 4
1000 pts → 2000 pts → 8000 patients → 400,000 patients

NEW: Fail fast and early

Trial 1 → FAIL
Trial 2 → FAIL
Trial 3 → FAIL
Trial 4 → PASS
Three shifts in paradigm: THREE

OLD: Personalize LATE

NEW: Personalize EARLY

RESPONDERS VS NON-RESPONDERS

TRIAL
N OF ONE trials

DENSE GENOMIC ANNOTATION

PERSONALIZED PRECISION MEDICINE
FROM GENES TO PHYSIOLOGY

Epigenes → Aza-Cytidine

Immune system → CTLA-4/ Yervoy

Blood Vessels → VEGF/Avastin

Stem cells

Metastasis

Stromal cells
“I need to know what it is that I am fighting”

- GIST patient

He lost me for some stretches […] but apparently pre-oncogenes […] reside in our genes, always, from birth, and when the right set of mutations hit us, provoked most often by carcinogens such as tobacco, asbestos, etc., cancer begins its long trudge toward metastasis.

- Scott

Are there Cliff Notes to this book?

- by email