FORTUNE
フォーチュン誌特約

なぜアメリカ人はがんで死に続けるのか？

衝撃の事実！
がん治療先進国アメリカの敗北

アメリカ政府が「がんとの戦争」を宣言してから 30 年あまり。
がんの犠牲者はいっこうに減っていない。
莫大な研究費を投じながら、なぜ画期的治療法が見つからないのか。
なぜ効かない新薬が次々と認可されるのか。
その理由がここにある。

クリフトン・リーフ ＝ 文
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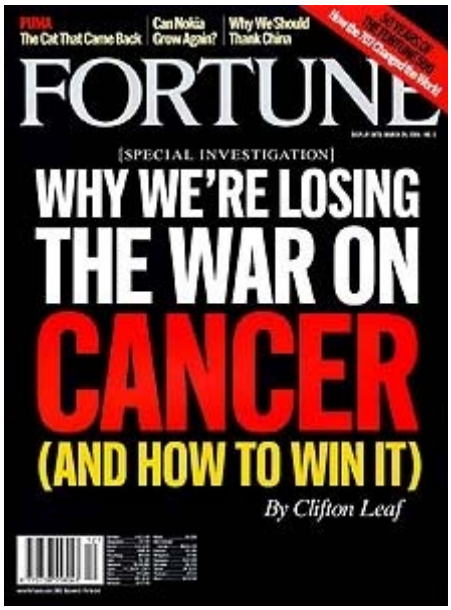
「がんとの戦い」で我々がほとんど進歩していないのはなぜだろう？



愛する人がこの恐ろしい病を克服するのを間近に見てきた人、睾丸がんを克服したランス・アームストロングのツール・ド・フランス 5 連覇に感嘆した人、あるいは、がんの治療法確立までもう一息と書かれた資金集めの手紙を受け取った人にとって、こうした質問は心外だろう。メディアは最近、「グリベック」、「ハーセプチン」、「イレッサ」、「アービタックス」、そして承認されたばかりの「アバスチン」といった画期的ながん治療薬について書き立てており、治療法の確立がこれまでになく現実味を帯びてきたように思われる。

しかし、**事実は異なる**。この戦いに絶対必要な希望と楽観が、極めて現実的で波及的な影響を持つ問題を見えにくくしているのだ。そしてこうした問題によって、この複雑で捉えどころがなく残忍な敵の根絶は一層困難なものとなっている。

1971 年に米国がん法（National Cancer Act）が制定されて以来、かなりの成果が上がっているものの、現状はいまだ勝利と呼ぶには程遠い。あまりに程遠いため、負け戦のようにさえ見える。

犠牲者数を見ると、がんは 2004 年に 56 万 3,700 人もの家族、友人、同僚、そして我が同胞であるアメリカ人の命を奪うと予想される。向こう 14 ヵ月間のがんによるアメリカ人の死亡者数は、この国のこれまですべての戦争犠牲者数よりも多いだろう。過去 30 年間で、がんの研究や治療法は大幅に進展し、投じられる資金も劇的に増加したにもかかわらず、がんによる年間死亡者数は 73%も増加した。これはアメリカの人口増加率の 1.5 倍に相当するスピードである。

国立がん研究所（NCI）および疾病対策予防センターの予想によると、今後 10 年以内にアメリカ人の死因のトップは心臓病からがんに替わる公算が大きい。75 歳以下の層では、がんはすでに死因のトップである。45 歳から 64 歳までの層では、がんによる死亡者数は心臓病、事故、卒中による死亡者数の合計を上回る。また、子供や 30 代、およびその間の層についても、最大の死因となっている。

人間の寿命が延びており、年齢とともにがんが増えるため、研究成果を評価する際に死亡者数の生の数値を取り上げるのはフェアではないと研究者は指摘する。よって、研究者は死亡率を計算する際に、長期間にわたる年齢層別のがん死亡者数を比較できるように死亡者数を調整している。しかし、こうした分析手法（高齢者の人口比率をニクソン政権時代と同程度として調整する）を用いても、アメリカ人ががんで死亡する比率は 1970 年代、そして 1950 年代とほとんど変わりないのである。がんによる死亡率を、患者の大半が高齢者である心臓病や卒中といった病気の死亡率と比べると、暗澹たる思いは一層深まる。この 50 年間で年齢調整後の心臓病の死亡率は 59%、卒中では 69%も減少しているのである。

この何十年間を通じてなぜ、この闘いに勝てていないのだろうか？そしてこうした状況を好転させるにはどうしたらいいのだろうか？

私はこの質問を数多くの人達にぶつけてきた。全米のがん治療で有名な病院の何十人もの研究者、医師、疫学者、製薬会社や研究所の薬理学者、生物学者、遺伝学者、食品医薬品局（FDA）、NCI、国立衛生研究所（NIH）の役員、資金団体、活動家、患者などである。ヒューストン、ボストン、ニューヨーク、サンフランシスコ、ワシントン D.C.をはじめとするがん研究拠点で 3 ヵ月にわたりインタビューを重ねるなかで、極めて優秀で真剣に仕事に取り組む人々に出会った。大半の人々は、がん研究の進展について楽観的な見方をしており、暗い統計結果は今日までに勝ち得た豊富な知識を適切に反映していないと述べている。こうした知識が、がんとして分類される 100 余りの病気の現実的な治療法にいつの日か結びつくと彼らは考えている。大半の人は研究方法について不安を抱くことも多いが、正しい方向に向かっていると感じていた。

しかし、これらの専門家のほぼ全員が、がん研究者が共有する集団思考は機能不全に陥っていると証言した。この集団思考のもとで、何万人もの医師や科学者は真の大発見では

なく、治療で小さな前進を図ることを目指すようになり、問題解決方法は協力に基づくものではなく、孤立した（重複した）ものになった。また、学術的な成果と発表が何に増して重視されるようになってしまった。

基礎科学から実際の患者の治療に至るすべての段階で研究者が頼っているのは、人に対する薬の効き目の予想という点で信頼できない実験モデルである。何百ものがん治療薬候補が開発対象となり、その多くがFDA（米国食品医薬品局）に承認されても、臨床試験で証明されたそうした医薬品の「効能」ががん治療にほとんど役立っていない現状を見れば、これは明らかだ。

がん研究の構造的問題

確かに、がんは他とは一線を画す難題である。この病気はそのアイデンティを変える不可解な能力を持つ。「がん細胞の特徴は遺伝子的な不安定さにある」とヒューストンのM.D.アンダーソンがんセンターのがん生物学部教授、アイザイア・“ジョシュ”・フィドラーは言う。がん細胞のDNAは正常な細胞のようには固定されていない。正常な細胞はその30億文字のコードをそのまま次世代のひとつひとつの細胞に伝えていく。しかし、がん細胞は分裂すると、そのDNA情報を変更した形で伝える可能性がある。そしてそれがほんのわずかな変更であっても、細胞の行動に非常に大きな影響を及ぼす可能性がある。よって、がんは突然変異したひとつの細胞から始まると考えられているが、最終的に形成される腫瘍は様々な気まぐれな特質を持つ無数の細胞から成っているとフィドラーは述べており、「腫瘍の遺伝子が様々に異なることが治療の非常に大きな障害になっている」と述べている。

ニューヨーク市のメモリアル・スローン・ケタリングがんセンターの所長であるハロルド・ヴァーマスほど、この問題に様々な角度から取り組んできた研究者はいないだろう。彼は「がんは非常に難しい問題を多数抱えた病気である」と述べている。彼は1976年に初めてがん遺伝子（突然変異時にがんを引き起こす可能性がある正常な遺伝子）を発見し、1989年にノーベル賞を共同受賞した。「がんとの闘い」が始まって5年目のこの貴重な発見は、がんが突然変異した遺伝子によって引き起こされるとの学説の確立に貢献した。後にヴァーマスはがん研究資金が大幅に増加したクリントン政権下でNIHのディレクターを務めた。「振り返ってみると、あっという間の出来事に思える」と彼は言う。「人類はこの30年間で、がんの発生についてのまったくの無知から、かなりの知識を持つ段階まで来たと思う」と彼は述べている。

しかしながら、こうした知識はすべて犠牲のうえに成り立っている。そして、こうした犠牲は余りに高くついたとの声は根強い。

ニクソン大統領は1971年の一般教書演説でちょうど100ワードを割き、「がんの治療法を発見するための集中キャンペーン」を提唱した。「戦い」という言葉は演説のなかでは使われなかったものの、その後数ヵ月間のうちにその言葉は大きく取り上げられるようになった。国立のがん研究機関が大きな中央集権的な力を発揮できるようにロビイストによ

る戦いが始まったのだ。一般教書演説が行われてから12月にNational Cancer Actが実際に調印されるまでの間に、マスコミが見出しに掲げたように、「創造的な研究」と「構造的な研究」のどちらを柱に据えるかで議論が巻き起こった。実質的にすべての医学会、医学部、および当時の3大がん病院（メモリアル・スローン・ケタリング、M.D.アンダーソン、およびバッファローのロズウェル・パーク）はこぞって連邦政府による資金を歓迎したが、指図は望まず、緩やかな調整だけで十分だとの意思を表明した。

一方、がん研究のゴッドファーザーとして知られるボストンの医師シドニー・ファーバーは、大規模で組織的ながん撲滅運動を展開するために公の支援を必要としていた。彼は「完全にがんを理解するまでとても待てない。今年死亡する可能性が高い32万5,000人のがん患者には時間がない。がん治療を前進させるのに基礎研究のすべての問題を解決する必要はない」と述べた。ファーバーはその秋、議会の公聴会で「医学の歴史を振り返れば、ワクチンからジギタリス療法、アスピリンに至るまで、作用機序が分からないまま、何十年、何百年にもわたって使われてきた治療法は枚挙にいとまがない」と証言したが、彼の意見は認められなかった。

今日、がん研究は完全に細分化されている。そのため、こうした研究を支える資金がどこから出ているのかを追跡するのはほとんど不可能と思われる。しかしとにかくやってみよう。

まずNCIの予算から見てみよう。議会が策定した今年のがん研究予算は47億4,000万ドルである。これは昨年の予算をわずか3.3%上回るに過ぎないとの不満が批評家から聞かれるが、政府は別のところで並外れた予算を組んでおり、この事実はほとんど知られていないようだ。実質的にNCIを管轄しているNIHは今年、国立環境衛生科学研究所（NIEHS）やその他のほとんど知られてない助成金交付の枠組みを通じて、がん研究にさらに9億900万ドルを拠出する予定である。復員軍人援護局はがん研究と予防に2003年の4億5,700万ドルを若干上回る金額をつぎ込む公算が大きい。疾病対策センター（CDC）は約3億1,400万ドルを福祉と教育のために拠出するものとみられる。国防総省でさえ、がん研究に資金を提供しており、乳がん、前立腺がん、卵巣がんの研究のために、同僚の研究者が審査する500件近い研究の助成金として今年2億4,900万ドルを拠出する。

州政府も予算を組んでいる。州知事が1997年から2003年までの間に署名したがん関連の予算は89件にのぼる。加えて、がん関連のチャリティー、がんセンター、および研究病院は今年、最近の税制改革に基づいて、総額20億ドルの寄付を集めるものと思われる。そしてもちろん、研究開発に巨費を投じている大手製薬会社の存在を忘れることはできない。タフツ医薬品開発研究センターの推定によると、製薬会社は約74億ドル、つまり年間研究開発費の約4分の1をがん、代謝性疾患、および内分泌障害治療薬の開発に当てるという。すべてを合算すると、アメリカ人は税金、寄付、民間企業の研究開発を通じて1971年以降、インフレ調整後で2,000億ドル近くをつぎ込んでいる計算になる。こうした国家レベルでの投資によってこれまでに何が得られたのか？

NCI のオンライン・データベースである「PubMed」によると、がん研究機関がこれまでに出版した文書は 156 万ページに及ぶという。そのうち大半は人の細胞の複雑な回路やそれに関連する遺伝子についてのもので、長年にわたり何百という雑誌に掲載されてきた。多くの発見は毎年開催される 100 を超える国際会議やシンポジウムで発表されている。

しかし、どういう訳か、どこかで重要な何かが失われてしまった。知識の探求が目的のための手段ではなく、目的そのものとなってしまったのだ。研究対象はますます狭い分野に限られ、そのため、がんや人間を全体として体系的に捉えようとする医師や科学者、あるいはまったく新しいアプローチを取ろうとする者は助成金を得ることが困難になっている。

例えば、RO1 と呼ばれる NCI 最大の助成金プログラムを例に挙げよう。この助成金の金額は 2003 年では平均 1 件当たり 33 万 8,000 ドルと寛大である。そして応募者の倍率は 3 倍と、獲得するのが最も容易な助成金のひとつとなっている。しかし、助成金の大半を獲得するのは、がん細胞やその他の細胞のなかのある特定の遺伝子あるいは分子構造を重点的に研究する研究者である。研究対象の範囲が狭ければ狭いほど、研究者が獲得する金額は大きくなるように思われる。

PubMed のデータベース検索によると、がん研究機関はマウスを使った実験的な研究を 15 万 855 件も発表している。このうち、がん治療に結びついたのは何件あったのだろうか？極めて少数である。「がんとの闘い」がどこで道を踏み誤ったかを理解したいなら、マウスを使った実験から検証を始めるのがいいだろう。

マウスモデルにどれだけの意味が？

ランダーはマサチューセッツ州ケンブリッジのホワイトヘッド研究所ゲノム研究センターのカリスマ的な創設者であり、ヒトゲノム・プロジェクトのリーダーである。フォーチュン誌がかつて「ヌクレオチドの王子」と呼んだ彼は、最寄りのスターバックスへの道順を教えるかのように、がん治療への生物学的な道筋を説明する。「例えば、遺伝子はたった 3 万個しかないとする。それらは限られた数の仕事しかしない。がんが有するメカニズムの数は無限ではなく、限りがある。限られたとは言うものの、確かにこれはかなり大きな数字であり、事実をわい小化するつもりはない。がんが使うメカニズムは 100 あるかもしれないが、100 は 100 に過ぎないということだ」。

がんを助長するマウスの遺伝子をひとつひとつ不活性化することで、こうしたメカニズムを孤立化させる攻撃をしかけ、その後、変異細胞を死滅させる薬を試験する必要があると彼は続けた。「これらは実行可能な実験だ」と彼は言う。「突然変異はがん細胞に弱点をも、もたらした。合理的ながん治療法として、がんの新しい突然変異すべてに関連した弱点がまもなく発見されるだろう」。

原則的には、こうした考えはおそらく正しいと思われる。しかし一方で、プロセス自体に重大な弱点がひとつある。マウスのひとつの遺伝子は人のひとつの遺伝子に非常に似ているかもしれないが、それ以外の点ではマウスと人はまったく異なるのだ。

「マウスモデル」を使った研究を行っている多くのがん研究者がこうした事実を忘れるか、無視していると思われる現実に、ロバート・ワインバーグはうんざりしている。マサチューセッツ工科大学の生物学教授で、人のがん遺伝子、および腫瘍抑制遺伝子の発見で「National Medal of Science」賞を授賞したワインバーグはとても生真面目な学者である。小柄で口ひげをたくわえた彼はごちゃごちゃとしたオフィスの真ん中にどうにか据えられたソファにドスンと座ると、講義を始めた。

「人のがんを研究するのに最もよく使用される実験モデルのひとつは、ペトリ皿で培養した人のがん細胞を取り出し、免疫力がないマウスに移植し、腫瘍を形成させ、結果として得られた異種移植片に人のがんに有効と思われる様々な薬を投与したものです。これは臨床前モデルと呼ばれます」とワインバーグは説明する。「そして、人のがんの臨床前モデルの多くが、患者の実際の腫瘍の反応をほとんど予見できないことがここ 10 年以上、ことによると 20 年くらいの間よく知られるようになりました」。マウスと人は遺伝子と臓器が似通っていても、心理面、細胞組織、代謝速度、免疫機能、分子シグナルなどに大きな違いがあると彼は言う。よって、遺伝子の同じスイッチが入れられたとしても、発生する腫瘍は大きく異なるのだ。

そこから数マイル離れたところで、ブルース・チャブナーもモデルに不満を抱いていた。ハーバード大学の医学部教授であり、マサチューセッツ・ゼネラル・ホスピタルがんセンターの臨床部長である彼は、研究者がマウスに発生させるいわば「即席腫瘍」は、様々な生物学的理由により、人間のがんの最も重大で恐ろしい特徴である、急速に変化する DNA を再現できないと述べている。前述したように、こうした特徴こそが、最も恐ろしい腫瘍に見られる並外れた複雑さをもたらしているのである。

「マウスの高血圧を治療する化合物が発見されれば、それは人にも効果があると思われる。どの程度の毒性があるかはわからないが、多分効くだろう」と、長年にわたり NCI のがん治療部門を統括してきたチャブナーは言う。つまり研究者は、遺伝子を「ノックアウト」（つまり不活性化する）したり、あるいはマウスに移植してがんを発生させたりと、がんに対してずっと同じアプローチを取っているのだ。「そして、肺がんのモデルができたと喜ぶ研究者がいるが、それは間違っている。人の肺がんには 100 個の突然変異があるからだ」と彼は言う。「遺伝子的に見れば、これほど複雑なものはほかにないだろう」。

イーライリリーでがん研究と臨床試験を統括していたホーマー・ピースは現在、製薬会社のリサーチフェローであり、人に対する薬の効力を見極めるうえでマウスモデルは実に不十分であることに同意する。「治癒された何百万、何千万のマウスを、転移疾患の臨床治療における比較的成功した例、あるいは失敗例と比べれば、こうしたモデルに何らかの欠陥があるに違いないと思うだろう」と彼は言う。

サウス・サンフランシスコのジェネテック社で分子腫瘍学研究のバイスプレジデントを務めるビシュヴァ・ディキシットは、「業界および学界の研究者の 99%が異種移植片を使用している」ことにより大きな危機感を抱いている。なぜこれほどまでにマウスモデルが使

用されるのか？答えは簡単だ。「手ごろで扱いやすい」からだとディキシットは説明する。「見るだけで腫瘍の大きさが分かるのだから」。

製薬会社はこうした問題を明らかに認識しているが、解決していない。「手ごろで扱いやすいという理由だけでこうしたモデルに毎年何億ドルもの金を使っているなら」、製薬会社はこの問題を解決すべきだとワインバーグは言う。

さらに気が滅入るのは、こうした不完全なモデルに頼っているせいで、人に効く薬を研究者が見落とす可能性があることだ。マウスのがん細胞を破壊した数多くの有望な薬が人に効かなかったのなら、マウスに効かなくても人には効く薬があるかもしれないということだ。つまり、過去 20 年間に開発が中止された何十万もの化合物のうち、人に本当に効果があるものがいくつもあったかもしれない。法廷と M.D.アンダーソンの患者の間を行き来し、イレッサや他の肺がん向けの分子標的治療を巡る大きな裁判で調査を担当するロイ・ハーブストは、こうしたことが起こる確率はかなり高いと確信している。「これはかなり気掛かりな問題だ」と彼は言う。「単独療法では効果が出ないものや、実験の条件が正しくなかったものや、正しい標的を見つけることができなかったために、多くの化合物を見過ごしてきた可能性がある」。

誰もが問題があると認識していながら、なぜ何の手立ても講じられていないのか？ワインバーグによると理由はふたつあるという。ひとつはマウスに代わるモデルがないということ。もうひとつは、「こうしたモデルを薬の有効性を見極める判断基準であると FDA が認識し続けているため、一種の惰性が形成されてしまった」ためだと言う。

なぜ「転移」の研究がなされないのか

因果関係が不明な多くの問題が、がん研究の足かせとなっている。どちらが先だったのか？薬の有効性を判断するための FDA の不完全な判断基準か、それとも薬をテストするための製薬会社の不完全なモデルか？

こうした疑問が投げかけられるのは、不完全な動物モデルのせいで、研究者に人の腫瘍も治癒できるとの誤った期待を抱かせる開発初期段階だけではない。FDA が患者の症状改善を裏付けるデータを探す臨床試験最終段階にも同様の疑問が当てはまる。そして、こちらの影響のほうがより重大だ。この場合の不完全なモデルとは腫瘍の緩解と呼ばれるものだ。

マウスや人の腫瘍が縮小し、それが薬の作用で起こっていることを確認できれば胸が躍る。腫瘍の縮小が良い兆候であるのは間違いないからだ。よって、これが大半の臨床試験の主な評価項目や目標のひとつになっていることは容易に理解できる。目で見て分かり、測定可能な目標であることが大きな理由である（がんの新薬についての新聞記事で「反応」と書いてあれば、それは腫瘍の縮小を指す）。

しかし、マウスモデルと同様に、腫瘍の緩解自体は、実際には病気の改善を正確に予見するものではない。化学療法や放射線療法で腫瘍が縮小することは度々ある。これによって外科手術によるがんの摘出が容易になるケースもある。そうでなくても、少なくともあ

る程度の時間稼ぎにはなるだろう。しかし残念なことに、がんに侵された細胞が一つ残らず切除されない限り、緩解が見られても患者の生存率は改善しない公算が大きい。

というのは、腫瘍が極めて悪性であると診断された時、すでに 10 億個以上の細胞を持つブドウ程度の大きさになっていることが多いためである。発見される前に、こうしたがん細胞の一部はすでに分裂し、体の他の部分へと移動を始めている可能性が高い。これを転移という。

こうした細胞の大半は他の細胞や器官に定着しない。血流の激流に入った転移細胞は生き残りを賭けた苦しい戦いを余儀なくされる。しかし、転移のプロセスは始まっており、10 億個もの細胞は狂ったように分裂して増殖し、血流の中を進もうとする。そしてもちろん、一部は転移に成功する。

最終的にがん患者を死に至らしめるのは局所的な腫瘍ではなく、転移のプロセスである。死因の実に 90%が転移なのである。活発な細胞が骨、肝臓、肺、脳、その他の致命的な部分に広がり、大きな打撃をもたらすのだ。

がん研究者はこのたちの悪い現象を押さえ込もうと長年にわたり努力し、複雑な転移メカニズムについて研究を重ねてきたと読者は考えるだろう。ところが現実はそうではないのだ。1972 年以降の NCI の助成金に関するフォーチュン誌の調査によると、例えば特定のがん（乳がんや前立腺がんなど）における転移の役割や、プロセスそのものの理解を目的とした転移に焦点を当てた研究提案は全体の 0.5%にも満たなかった。昨年 NCI の助成金を獲得した 8,900 件近い研究提案のうち、92%には転移という言葉すら使われていなかったのだ。

転移が軽くあしらわれているのは、「難解だから」と M.D.アンダーソンのジョシュ・フィドラーは述べている。「難しいことを研究しても見返りがないからね」。そしてこう付け加えた。「助成金の審査員は焦点を絞った研究提案を好む傾向にある。例えば、この抗体を使ってこうする、ああするとまくしたてれば、たぶん助成金をもらえるだろう」。

転移は広範囲にわたる概念である。体の隅々にまで及ぶ現象で何十というプロセスから成り立っている可能性がある。これほど可変要因が多い現象について反復可能な実験を行うのは難しい。しかし、こうした研究こそが必要なのだ。だが、研究者は再現可能な結果を数多く生み出せる、より簡単な実験を選んでいるとワインバーグは言う。残念ながら「データが積み重なることで、研究者は何か意味のあることをしているという錯覚に陥ってしまう」と彼は述べている。

データを積み上げたいとの欲求は新薬開発の規制プロセスの核心にも影響している。FDA の使命は薬の発売を承認する前にその安全性と効能を確認することである。よって規制当局は、薬が臨床試験である程度有効だったという確固たるデータを確認する必要がある。しかし、そもそも、何かが起こるのを阻止するための「活動」を見るのは難しい。体内を循環するたんぱく質など、がん細胞が他の細胞に広がり始めたことを示す適切なバイオマーカーがあると思われるが、現時点ではそれが何なのかは分かっていない。

よって、当然のことながら、製薬会社は転移の問題（患者を死に至らしめている原因）を解決することには重点を置かず、腫瘍を縮小させる薬の開発（患者の死亡とは関係のない）に焦点を当てているのだ。

いずれにせよ、こうした薬の多くが承認を取得している。もちろん承認されない薬も多数ある。そしてFDAは相変わらず、「がんとの闘い」を長期化させていると非難されている。しかし、非があるのは審判ではなく、選手のほうだろう。なぜなら腫瘍を縮小させる薬の多くが標準的な治療法と同程度の効果しか示していないからである。

昨年8月にブリティッシュ・メディカル・ジャーナルで発表された重要な研究のショッキングな結果もこうした問題のある現状を裏付けている。イタリア人の二人の薬理学者が1995年から2000年までに欧州で承認された新しい12のがん治療薬の臨床試験結果を詳しく調査し、適応症ごとに標準的な治療法との比較を行った。その結果、生存率の改善、患者のクオリティ・オブ・ライフ（QOL）の改善、安全性の向上などの面で、いずれの新薬にも何ら大幅な優位性は認められなかった。しかし、これらの新薬はすべて、古い薬の何倍もの価格が付けられ、中には350倍のものさえあった。

なぜ新薬は期待はずれなのか

新薬開発で使用される不完全なモデル、腫瘍縮小についての執着、個々の細胞のメカニズムに注目するあまり体全体で起きていることをほとんど無視してしまうこと。こうした間違いはすべて臨床試験段階で顕在化する。臨床試験とは新薬やそのほかの医療プロセスを人でテストするための3段階から成る厳格に管理されたシステムだ。依然としてこれは新薬が研究段階を経て承認されるための唯一のプロセスであるが、このプロセスに不満を持たないがん研究者はいないだろう。

2003年2月、がんセンターの部長をはじめとする学識経験者の会議は、臨床試験が「長く、困難な」プロセスであり、規制に縛られていると結論付けた。大幅な改革や資金面での更なる支援がなければ、「このシステムは引き続き非効率で反応に乏しく、費用がかかりすぎる公算が大きい」と結論付けた。

患者はこの承認プロセスから得るものはほとんどないと考えている。成人がん患者のなんと97%が治験に参加しない現状を見ても、これは明らかだ。

臨床試験には大きな問題がふたつある。ひとつは、臨床試験費用の大半を負担する製薬会社には、試験対象の化合物として承認が得られる公算が大きいものを選ばざるをえない抗し難い動機がある点だ。これは試験期間が長期にわたり、莫大な費用がかかることからも明らかである。

さらに、この臨床試験システムにより製薬会社は最も重症の患者に最も有望な新化合物を試すことを余儀なくされる。こうした患者では薬の効果（例えば腫瘍の縮小）を見るのは比較的容易だが治癒はほぼ不可能である。その時点ではすでにがんは広がりすぎており、腫瘍はかなりの遺伝子突然変異を起こしている。よって、初期段階の患者には効き目があ

るかもしれない薬が承認されるチャンスは永久に失われる（有望とされてきた新薬が結局期待はずれとなっている大きな原因のひとつは、これかもしれない）。

ふたつ目の問題はさらに深刻だ。臨床試験の目標が、人の命を救うことではなく、「適切な」科学を行うという見当違いのものになっている点である。これは悪い治療を行っているという意味ではない。治験に参加した患者は特に丁寧な治療を受けている。しかし、治験の本当の目標は、治療 X は治療 Y よりも優れているといった仮説を立証することにある。そして、残念なことに、この非常に長い治験プロセスによって得られた情報がほとんど何の役にも立っていないケースが多いのだ。新薬が既存の治療法よりも平均 10%多く腫瘍を縮小することを 10 年以上かけて発見したとしても、どれほど多くの人の命がこれで助かるのだろうか？

直腸結腸がん治療薬として 2 月に承認された 2 つの新薬、「アービタックス」と「アバスチン」を例にとろう。いずれについても、臨床試験に必要な患者数を登録するだけで何ヵ月を要した。その後、治験に参加した医師は事前に設定されたうんざりするような手順に従い、投薬を行い、膨大なデータを集めていく（イムクローン社と FDA の有名なトラブルは臨床試験を適切に設定しなかったことから発生した）。

そして臨床医学者が長年にわたる臨床試験から得たのは、標準的な化学療法の投薬計画にアバスチンを加えると末期の結腸直腸がん患者約 400 人に平均 4.7 ヵ月の延命効果が見られたということである（これに先立つ乳がん患者への治験は失敗した）。この病気の末期患者は通常 16 ヵ月以上は生存しないことから、腫瘍学者はこうした効果をかなり顕著なものと考えている。

そしてアービタックスであるが、これは確かに腫瘍を縮小するものの、延命効果はまったく示していない。なかには同薬で良好な結果を得た患者もいたが、治験グループの平均延命率に変化はなかった。それでも、アービタックスは主に、すでに承認されているほかの治療法がすべて効果がなかった場合の併用療法として承認されたのだ。1 週間当たりの投与費用は 2,400 ドルである。

同様のことがアストラゼネカのイレッサについても言える。イレッサは新たな生物製剤特効薬であり、がん細胞の分子レベルの信号伝達を阻害するように開発された化合物である。イレッサが症状の緩和や生存率の向上といった患者のためになる効能を持つことを示した治験はひとつもなかった。このことはアストラゼネカが強気のプレスリリースのなかで、当然の事のように認めた事実である。それでも FDA は、治験に参加した患者の 10%に腫瘍に縮小がみられたと述べ、昨年、ある種の肺がんに対する最後の手段として同薬を使用することを承認した。

「非常に優秀で資金も豊富な研究者が世界中で 1 万人以上の患者を対象に、こうした新しい分子標的薬剤の臨床試験を実施した」とダナファーバーがん研究所のブルース・ジョンソンは言う。「アストラゼネカはイレッサを試験した。アイシス・ファーマスーティカル

ズとイーライリリーはアイシス 3521 と呼ばれる化合物を試験した。いくつもの企業が数千万ドルもの資金を投じたが、結局、何の成果も得られなかったのだ」。

何らかの明らかな成果を上げた分子標的薬剤はノバルティス ファーマの「グリベック」である。これは腫瘍を抑制するだけでなく、救命効果も示している。慢性骨髄性白血病（CNL）という珍しい白血病や、消化管間質腫瘍（GIST）というさらに稀な胃がんに劇的な有効性を示している。初期段階の報告は、ほかの 3 つのがんにも程度の差こそあれ有効性があるようだと述べている。グリベックの成功は、長年にわたる「がんとの闘い」で我々が取ってきた戦略が正しかったことを立証するものと考えられている。

しかし、グリベックですら、当初の期待とは異なるものだった。CML は複雑ながんではない。この病気では、たったひとつの遺伝子変異によって、がん細胞の増殖シグナルの伝達が引き起こされる。グリベックは巧みにこの致命的なシグナル伝達を遮断する。ちなみに一般的ながんでは 5〜10 個程度の遺伝子変異がみられることが多い。もうひとつ言えることは、「単純な」がんですら、賢くなるということだ。（生涯服用しなければならない）薬に長年さらされている悪性細胞は、グリベックが阻害する細胞内シグナルの伝達系を変異させ、薬剤耐性を獲得する。

道理で、がんは心臓病よりもずっと厄介な病気であるわけだ。ジェネテックのコマーシャル・ダイアグノスティック部門のシニア・ディレクター、ボブ・コーヘンは「複数の進展はないだろう」と言う。完全には腫瘍を破壊しない薬を使うと、（生き残った）細胞から異質性が進化して、“回りのことなんかどうでもいい！こんな薬にめちゃくちゃにされてたまるか！”などと言い出す。そこで研究者は突如としてこうした複雑なメカニズムを手なずけようと、細かく分析し始めた。これが現状だ」そして、こうした理由から、早期に複数の方法によって攻撃を加えることしか、この病気を退治できるチャンスはないのである。

3 剤、4 剤、5 剤と複数の薬を使用する併用療法という治療法がある。もちろん、こうした実験的な化合物のカクテル療法は、医師が HIV をコントロールするために使用した方法である。HIV の急速に変異するウイルスはかっては死刑宣告を意味していた。今回インタビューしたほぼすべての臨床医学者および科学者は、同様のアプローチが新世代の抗がん剤に必要だと考えている。しかし、ここでも、がん研究の組織的な力関係がこうした開発をほとんど不可能なものにしている。

承認されていない複数の薬を臨床試験で併用すると、製薬会社は法的および規制にかかわる問題を多く抱えることになり、安穏とはしていられない。製薬会社に勤務する多くの腫瘍学者は、政府やがんセンターの研究者と同様に一般大衆の健康のために努力を重ねているが、新しいアイデアを試すことにはやや消極的かもしれない。結局のところ製薬会社の望みは、治験中の化合物が FDA に承認されることなのだ。2〜3 の承認されていない薬がいっしょに試験される場合、どの薬に効果があり、どれにないのか、また服作用の原因はそのうちの 1 つの薬なのか、あるいは組み合わせによるものかを見極めるのはより困難で

ある。「データベースの管理、結果の解釈、データの所有という点からみれば、困難さは一段と増す」とイーライリリーのピースは付け加えた。

がんについての考え方を一新する

奇妙に聞こえるかもしれないが、これまでの多くの失敗、そしてさらに重要なことに今後の勝利にとって、がんの定義は重要な意味を持つ。約2,400年前のギリシャの医師ヒポクラテスは、がんを、体中に広がり「カニの足のように」体のほかの部分をつかんでしまう病気と述べた。同様に、今日の医学の教科書には、がんは増殖している腫瘍細胞が、細胞同士の間にある薄いたんぱく質でできた基底膜を押し破るときに始まると書かれている。がんになるためには、悪性細胞が体のほかの部分を侵略しなければならないとは、なんともしゃれた言い方だ。

ダートマス・メディカルス・スクールの薬理学および医学教授であるマイケル・スポーンはこうした考え方を「まったくのナンセンス！」と切り捨てる。彼は続けて言う。「我々はがんのこうした定義に1890年から縛られている。私もメディカルスクールで、侵襲があるまではがんではないと教えられた。これはまるで、真っ赤な炎が納屋の屋根からふきあがるまでは火事とは呼べないと言っているのと同じだ」。

実際、がんはこれより早く始まっている。そしてこのことにこそ、がんを押さえ込む最良の戦略があると最近NCIから「Eminent Scholar」の称号を受けたスポーンは考えている。長年にわたり我々のなかでくすぶり続けている燃えかすを積極的に探し出し、大きな火事になる前に消し止めようではないか、と。まず、がんが命にかかわる悪性の段階に入るのを防ぐのだ。

30年以上NCIに勤務したスポーンは、研究者のがんに対する考え方を変えるべく、長年尽力している。がんを、急速に増殖する細胞からなる侵略的なグループという「状態」ではなく、発ガンと呼ばれる「プロセス」と見なしてほしいのだ。スポーンによると、がんは様々な細胞形質転換や時には長い潜伏期間を経て発現する多段階の病気なのだ。

よって、特に病変（医師には形成異常、異常増殖、前がん状態として知られる）が起きた重大な局面では、こうしたプロセスを初期段階で阻害することが鍵を握ると考えられる。これを行うには医療関係者が、発がんの初期段階にある人は「健康」で治療に及ばずとの考えを捨てる必要がある。がんに向かって進んでいる人は健康ではないのだ。

この理論は至極まっとうであるうえ、今すぐ始められる点でも素晴らしい。前がん状態の細胞変異は様々な種類のがんへの進行を意味する。こうした変異の多くは比較的容易に発見でき、取り除くことができる。また、既存の薬や治療法で症状を改善できるものも多い。

最適な例としてパップスメア（子宮がん検査）が挙げられる。これは子宮頚管の細胞の前がん変化を発見するための検査だ。こうした簡単な検査、そしてこれに続いて病変部位の外科的摘出が1950年代に始まって以来、子宮頸がんの罹患率と死亡率はそれぞれ78%と

79%も低下した。パップスメアが実施されていない国では子宮頸がんは女性の主要な死因のひとつとなっている。

結腸がんについても同じことが言える。結腸の腺腫性ポリープ（器官内膜の病変）のすべてが悪性で侵襲的なものになるとは限らない。しかし、結腸がんはこうした異常なプロセスを経てはじめて致命的なものとなるのである。バレット食道（がんの前兆）から角質増殖（頭と首のがん）まで、形成異常に似た状態は枚挙にいとまがない。確かに一部のがんについてはこうした検査が行われているが、その範囲を大幅に拡大していくことが必要だ。

発がんを示唆するバイオマーカーは、その精度が高まってはいるものの、信頼性が高いというには程遠いとの不満の声や、もっと詳しい情報が得られるまで結論を出すのは控えるべきだといった意見が一部に聞かれる（聞き覚えがあるコメントだ・・・）。一方、心臓病の研究者は正反対のやり方で、がん研究を大幅に上回る成果を収めている。高コレステロールや高血圧だからといって必ずしも将来、循環器疾患にかかるとは限らないが、とりあえずこうした症状は治療の対象となるのだ。

より早く前兆を発見すること（前がん状態を示す血液、尿、あるいは皮膚標本中のたんぱく質の状態や、進行する公算が大きい極めて早期のがんの発見）で大きな成果を収めているがん研究者はほんの一握りである。例えば、NCI で病理学のヘッドを務めるランス・リオッタは、先端技術を用いた血液検査で卵巣がんを発見できることを示した。この検査では女性の血液中にある約 70 種類のたんぱく質に固有な「クラスタパターン」を識別することができる。「我々は以前には知られていなかった数多くのマーカーを発見した」と彼は言う。これにより数多くの人命を救える可能性がある。既存の薬で早期の卵巣がんは 90%以上が治癒可能であるが、末期では 75%が死亡する。早期のたんぱく質検査により膵臓がんの延命率も改善されているとリオッタは語った。

しかし、こうした戦略には費用がかかる。バイオマーカー、および早期病変（その大半が侵襲性のがんにはならない）を発見するための大規模な検査は医療制度の大きな負担となり、致命的ではない病変摘出のため危険を伴う外科手術が増加する可能性があるとの声も一部に聞かれる。だが、何もしないコストはもっと大きいことも確かである。

戦いに勝つために

この残酷な戦いについてのアメリカの認識を変えるには、がん研究者がこの病気の撲滅に一致団結することが必要である。個人ではなく集団でこの病に立ち向かうというシドニー・ファーバーの 33 年前の望みを叶えられる十分な知識を今日の医師や研究者は手にしているのである。

NCI は研究資金の提供方法を大幅に変えることで、こうした変化を起こすことができる。大局的な問題に焦点を当てた共同研究に NCI がより多くの資金を回すことで、R01（マウスを使用した無数の模倣実験を支えた助成金）によって形成された集団思考を白紙に戻すことができるのだ。NCI はすでに「SPORE」（「specialized programs of research excellence」の略称）と呼ばれるプログラムでこうした資金提供における方針の転換を実施し始めている。これらは異なる専門分野の研究者が協力してがんの様々な問題を解決しようというプログラムである。しかし、個人研究の助成金は同機関の研究予算の 4 分の 1 を占めており、SPORE 向け助成金の実に 12 倍以上に達している。NCI は基礎科学研究の金蔓であることを止めて、がん転移を阻止する方法や、人の反応に類似したより良い実験モデルを見つけ出すことなど、捉えどころのないこの病魔に徹底的な攻撃を仕掛けるために税金を使うべきである。

同時に NCI は、がんの成長を示すバイオマーカーの発見に全力を傾けるべきである。また、病気を回避あるいはコントロールできるチャンスを患者に与えてくれるような、簡単な血液検査や尿検査（例えば PSA 検査）、あるいは高度な分子画像技術（PET や CT スキャン）で分かるバイオマーカーの発見にも尽力すべきだ。さらに言えば、喫煙の習慣を止めさせるだけで、アメリカ国内で何万件ものがんを防ぐことができ、がんによる死亡を 30%減少させることができる。こうした明らかにまっとうな見解はインタビューしたすべての研究者から聞かれた。

残念ながら、これは百万ドルどころではなく、十億ドルに値するほどの挑戦だろう。しかし、アメリカではすでに研究費用として何十億ドルもの資金が投じられており、そのうえ 1 年間に治療費として 640 億ドルも金が支払われているのである。研究資金のシフトを円滑に進めるには、議会が国のがん研究資金の供給先を 5 つの国立機関から 1 つに絞る必要がある。がん研究は復員軍人援護局や国防総省ではなく、NCI が統括すべきである。

同様に重要なのは、がん研究をリードする学者、FDA、議員が、臨床試験と承認プロセスを転換させ、薬の効果についての情報がもっと早く患者に届くようにすることが必要だ。

臨床試験が患者に、単なる既存薬治療の改善と思われる以上の効果をもたらすことができれば、臨床試験に参加するがん患者は急増するだろう。参加率が上昇すれば、プロセスの進展は加速し、より多くの併用療法をより早く、より安く試験できるだろう。

しかし、どの薬が本当に有望かを見極めるには、さらにもうひとつ、やらなければならないことがある。それらの薬を病気があまり進行していない患者で試験することである。ここでも、がんの遺伝子的な不安定性が理由である。つまり病状の進行は、体に大きなダ

メージを与えるだけでなく、腫瘍に数多くの突然変異をもたらし、早期の患者とはかなり違った状態となるためだ。末期のがん患者であれば、早期のがんに効くとみられる薬はさほど効かないだろう。しかし、現在の多くの規則により、製薬会社は助けられる見込みの少ない患者で治験を行わざるを得ない状況にあり、唯一できることといえば、既存治療を少しでも上回る治療法を見つけることなのだ。現在、一部のがん患者を救える可能性がある薬の開発が中止されるのは、もともと助かる見込みがなかった患者をこの薬では助けられないという理由によるものだ。こうしたことは止めるべきである。

血管形成プロセスを阻害するために開発された新薬、つまり腫瘍に酸素と栄養素を供給する毛細血管の発達を阻害するように開発された化合物の状況を見てみよう。最も知られているのはアバスチンであるが、現在、約 40 もの血管新生阻害剤が臨床試験中である。

こうした薬の背景にあるのは、ここ何十年間、がん研究者が真剣に取り上げず、助成金もほとんど受けてこなかった考え方のひとつである。現在、ボストン小児病院の外科医であるジュダ・フォークマンがこうした概念を初めて唱えたのは 43 年前だ。海軍の研究所で人工血液を研究中に、彼は単純で一見して正しいと思われるアイデアがひらめいた。どの細胞も成長には酸素が必要であり、それはがん細胞とて同じことである。体内の酸素は血液によって運ばれるため、急速に成長する腫瘍も、血管へのアクセスなしには大きくなれないという考え方である。

後にフォークマンは、腫瘍は生体信号を送ることで新たな血管形成を促しているとの結論に至った。そうした成長信号を止めることができれば、腫瘍を飢えさせ、成長を阻止することができると推論した。彼は様々な医学雑誌に実験レポートを送ったが、ことごとく却下された。しかし、「ニューイングランド・ジャーナル・オブ・メディシン」の編集者がフォークマンの講義を聞き、1971 年に同誌のベスイスラエル病院セミナーのセクションに記事を掲載することを申し出た。1971 年というのは皮肉なことに「がんとの闘い」が始まった年である。

何十年もの抵抗の後、がん研究者はようやくフォークマンの考え方に同意するようになった。アバスチンを歓迎する反応がこうした変化を如実に語っている。しかし、早期段階の患者の治療に使用されて初めて、血管新生阻害剤はその最大の存在意義を示すことができる。腫瘍への血液供給を阻止するように開発された薬は、従来の毒性のある化学療法に比べ、作用するまでに、はるかに時間がかかる。末期の患者や進行が速いがん患者にはこのような時間はないだろう。加えて医師にはこれらの薬をいくつか併用できる自由も必要である。腫瘍はいくつかのシグナル伝達メカニズムによって血管新生を促すと研究者は考えている。よって最良のアプローチはいくつかの薬を用いて、すべてのルートを遮断することである。

正解は誰にも分からない。フォークマンが 40 年間取り組んできた概念から新たな治療の枠組みが生み出される可能性もある。しかし、単純で明白と思われるこうした転換を実現するには、新薬承認をコントロールしている規制から不法行為法や知的所有権に至るまで、

がん研究に関わるすべてが変わらなければならない。今日、科学は知識と手段を手に入れた。今度は我々が行動を起こす番だ。

※この記事は、PRESIDENT5.17 号掲載「衝撃の事実！がん治療先進国アメリカの敗北」の拡大版です。

FORTUNE

WHY WE'RE LOSING THE WAR ON CANCER [AND HOW TO WIN IT]

BY CLIFTON LEAF

Avastin, Erbitux, Gleevec . . . The new wonder drugs might make you think we're finally beating this dreaded scourge. We're not. Here's how to turn the fight around.

It's strange to think that I can still remember the smell after all this time. The year was 1978, not long after my 15th birthday, and I'd sneaked into my brother's bedroom. There, on a wall of shelves that stretched to the ceiling, were the heaviest books we had in our house—24 volumes of the *Encyclopedia Britannica*. The maroon spines were coated in a film of dust, I remember. The pages smelled as if a musty old pillow had been covered in mint.

I carefully pulled out the volume marked HALICARNASSUS TO IMMINGHAM and turned to the entry for Hodgkin's disease. It took forever to read the half-dozen paragraphs, the weighty book spread open on my lap like a Bible. There was talk of a mysterious "lymphatic system," of "granulomas" and "gamma rays," as though this disease—the one the doctor had just told me I had—was something out of science fiction. But the last line I understood all too well: Seventy-five percent of the people who got it would die within five years.

As it turns out, I did not die from Hodgkin's, though the cancer had already spread from my neck to my lungs and spleen. I lost my spleen to surgery and most of my hair to chemotherapy and radiation. But I was lucky enough to get into a clinical trial at the National Cancer Institute that was testing a new combination therapy—four toxic chemicals, together called MOPP, plus those invisible gamma rays, which flowed from an enormous cobalt 60 machine three stories below ground. The nurses who stuck needles in my arm were so kind I fell in love with them. The brilliant doctor who tattooed the borders of an imaginary box on my chest, then zapped me with radiation for four weeks, had warm pudgy hands and a comic look of inspiration, as though he'd thought of something funny just before entering the exam room. The American taxpayer even footed the bill.

Most of all, of course, I was lucky to survive. So it makes the question I am about to ask sound particularly ungrateful: Why have we made so little progress in the War on Cancer?

The question may come as a shock to anyone who has witnessed a loved one survive the dread disease—or marveled at Lance Armstrong powering to his fifth Tour de France victory after beating back testicular cancer, or received a fundraising letter saying that a cure is within our grasp. Most recently, with media reports celebrating such revolutionary cancer medicines as Gleevec, Herceptin, Iressa, Erbitux, and the just-approved Avastin, the cure has seemed closer than ever.

But it's not. Hope and optimism, so essential to this fight, have masked some very real systemic problems that have made this complex, elusive, relentless foe even harder to defeat. The result is that while there have been substantial achievements since the crusade began with the National Cancer Act in 1971, we are far from winning the war. So far away, in fact, that it looks like losing.

Optimism is essential, but the percentage of Americans dying from cancer is still what it was in 1970 … and in 1950.

Just count the bodies on the battlefield. In 2004, cancer will claim some 563,700 of your family, friends, co-workers, and countrymen. More Americans will die of cancer in the next 14 months than have perished in every war the nation has ever fought … *combined.* Even as research and treatment efforts have intensified over the past three decades and funding has soared dramatically, the annual death toll has risen 73%—over one and a half times as fast as the growth of the U.S. population.

Within the next decade, cancer is likely to replace heart disease as the leading cause of U.S. deaths, according to forecasts by the NCI and the Centers for Disease Control and Prevention. It is already the biggest killer of those under 75. Among those ages 45 to 64, cancer is responsible for more deaths than the next three causes (heart disease, accidents, and stroke) put together. It is also the leading disease killer of children, thirtysomethings—and everyone in between.

Researchers point out that people live a lot longer than they used to, and since cancer becomes more prevalent with age, it's unfair to look just at the raw numbers when assessing progress. So when they calculate the mortality rate, they adjust it to compare cancer fatalities by age group over time. But even using this analysis (in which the proportion of elderly is dialed back to what it was during the Nixon administration), the percentage of Americans dying from cancer is about the same as in 1970 … and in *1950*. The figures are all the more jarring when compared with those for heart disease and stroke—other ailments that strike mostly older Americans. Age-adjusted death rates for those diseases have been slashed by an extraordinary 59% and 69%, respectively, during the same half-century.

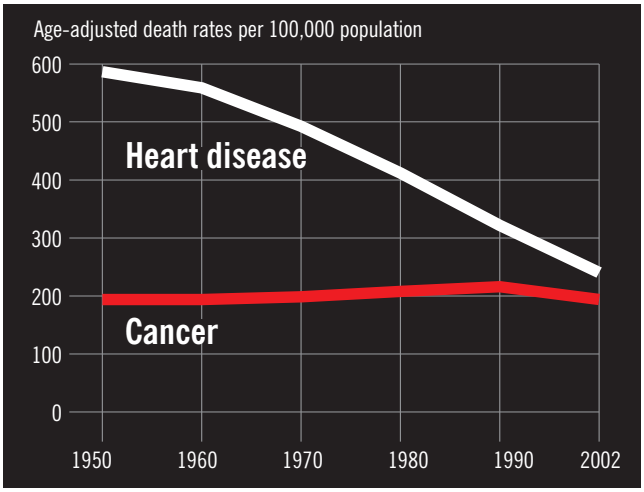
Researchers also say more people are surviving longer with cancer than ever. Yet here, too, the complete picture is more disappointing. Survival gains for the more common forms of cancer are measured in additional *months* of life, not years. The few dramatic increases in cure rates and patient longevity have come in a handful of less common malignancies—including Hodgkin's, some leukemias, carcinomas of the thyroid and testes, and most childhood cancers. (It's worth noting that many of these successes came in the early days of the War on Cancer.) Thirty-three years ago, fully half of cancer patients survived five years or more after diagnosis. The figure has crept up to about 63% today.

Yet very little of this modest gain is the result of exciting new compounds discovered by the NCI labs or the big cancer research centers—where nearly all the public's money goes. Instead, simple behavioral changes such as quitting smoking have helped lower the incidence of deadly lung cancer. More important, with the help of breast self-exams and mammography, PSA tests for prostate cancer, and other testing, we're catching more tumors earlier. Ruth Etzioni, a biostatistician at Seattle's Fred Hutchinson Cancer Research Center, points out that when you break down the Big Four cancers (lung, colon and rectal, breast, and prostate) by stage—that is, how far the malignant cells have spread—long-term survival for advanced cancer has barely budged since the 1970s (see charts opposite).

And the new cases keep coming. Even with a dip in the mid-1990s,

PUBLIC ENEMY NO. 1

Doctors have dramatically reduced deaths from heart disease. But cancer is as lethal as ever and may soon overtake it as the biggest killer of Americans.



FORTUNE CHART / SOURCE: CDC

the incidence rate has skyrocketed since the War on Cancer began. This year an additional 1.4 million Americans will have that most frightening of conversations with their doctor. One in two men and one in three women will get the disease during their lifetime. As a veteran Dana-Farber researcher sums up, "It is as if one World Trade Center tower were collapsing on our society every single day."

So why aren't we winning *this* decades-old war on terror—and what can we do now to turn it around?

That was the question I asked dozens of researchers, physicians, and epidemiologists at leading cancer hospitals around the country; pharmacologists, biologists, and geneticists at drug companies and research centers; officials at the FDA, NCI, and NIH; fundraisers, activists, and patients. During three months of interviews in Houston, Boston, New York, San Francisco, Washington, D.C., and other cancer hubs, I met many of the smartest and most deeply committed people I've ever known. The great majority, it should be said, were optimistic about the progress we're making, believing that the grim statistics belie the wealth of knowledge we've gained—knowledge, they say, that will someday lead to viable treatments for the 100-plus diseases we group as cancer. Most felt, despite their often profound misgivings about the way research is done, that we're on the right path.

Yet virtually all these experts offered testimony that, when taken together, describes a dysfunctional "cancer culture"—a groupthink that pushes tens of thousands of physicians and scientists toward the goal of finding the tiniest improvements in treatment rather than genuine breakthroughs; that fosters isolated (and redundant) problem solving instead of cooperation; and rewards academic achievement and publication over all else.

At each step along the way from basic science to patient bedside, investigators rely on models that are consistently lousy at predicting success—to the point where hundreds of cancer drugs are thrust into the pipeline, and many are approved by the FDA, even though their proven "activity" has little to do with curing cancer.

"It's like a Greek tragedy," observes Andy Grove, the chairman of Intel and a prostate-cancer survivor, who for years has tried to shake this cultural mindset as a member of several cancer advisory groups. "Everybody plays his individual part to perfection, everybody does what's right by his own life, and the total just doesn't work."

Tragedy, unfortunately, is the perfect word for it. Heroic figures battling forces greater than themselves. Needless death and destruction. But unlike Greek tragedy, where the Fates predetermine the outcome, the nation's cancer crusade didn't have to play out this way. And it doesn't have to stay this way.

"A VERY TOUGH SET OF PROBLEMS"

NUCLEAR FISSION WAS A MERE eight months old when the Panzers rolled into Poland in September 1939, beginning the Second World War. Niels Bohr had announced the discovery at a conference on theoretical physics at George Washington University. Three years later the crash program to build an atomic device from a uranium isotope began in earnest. And within three years of that—Aug. 6, 1945—a bomb named Little Boy exploded over Hiroshima.

NASA came into existence on Oct. 1, 1958. Eleven years later, two men were dancing on the moon. Sequencing the entire human genome took just 18 years from the time the idea was born at a small gathering of scientists in Santa Cruz, Calif. Go back as far as Watson and Crick, to the discovery of the structure of DNA, and the feat was still achieved in a mere half-century.

Cancer researchers hate such comparisons. Good science, say many, can't be managed. (Well, sure, maybe easy stuff like nuclear physics, rocket science, and genetics—but not cancer.)

And to be sure, cancer *is* a challenge like no other. The reason is that this killer has a truly uncanny ability to change its identity. "The hallmark of a cancer cell is its genetic instability," says Isaiah "Josh" Fidler, professor and chair of the department of cancer biology at Houston's M.D. Anderson Cancer Center. The cell's DNA is not fixed the way a normal cell's is. A normal cell passes on pristine copies of its three-billion-letter code to every next-generation cell. But when a cancer cell divides, it may pass along to its daughters an altered copy of its DNA instructions—and even the slightest change can have giant effects on cell behavior. The consequence, says Fidler, is that while cancer is thought to begin with a single cell that has mutated, the tumors eventually formed are made up of countless cellular cousins, with a variety of quirky traits, living side by side. "That heterogeneity of tumors is the major, major obstacle to easy therapy," he says.

Harold Varmus, president of Memorial Sloan-Kettering Cancer Center in New York City, agrees. "I just think this is a very tough set of problems," says Varmus, who has seen those problems from more angles than just about anybody. He shared a Nobel Prize for discovering the first oncogene (a normal gene that when mutated can cause cancer) in 1976. That crucial finding, five years into the War on Cancer, helped establish that cancers are caused by mutated genes. Later Varmus served as NIH director under Bill Clinton, presiding over a period of huge funding increases. "Time always looks shorter in retrospect," he says. "I think, hey, in 30 years mankind went from being almost completely ignorant about how cancer arises to being pretty damn knowledgeable."

Yet all that knowledge has come at a price. And there's a strong argument to be made that maybe that price has been too high.

President Nixon devoted exactly 100 words of his 1971 State of the Union speech to proposing "an intensive campaign to find a cure for cancer." The word "war" was never mentioned in the text, yet one would flare up in the months that followed—a lobbying war over how much centralized control the proposed national cancer authority would exert. Between the speech and the signing of the National Cancer Act that December, there was a "battle line between 'creative research' and 'structured research,' " as a news report headlined it. A massive alliance of virtually all the medical societies, the medical schools, the then–Big Three cancer hospitals (Memorial Sloan-Kettering, M.D. Anderson, and Roswell Park in Buffalo) said yes to federal money but wanted very little direction and only loose coordination from Uncle Sam.

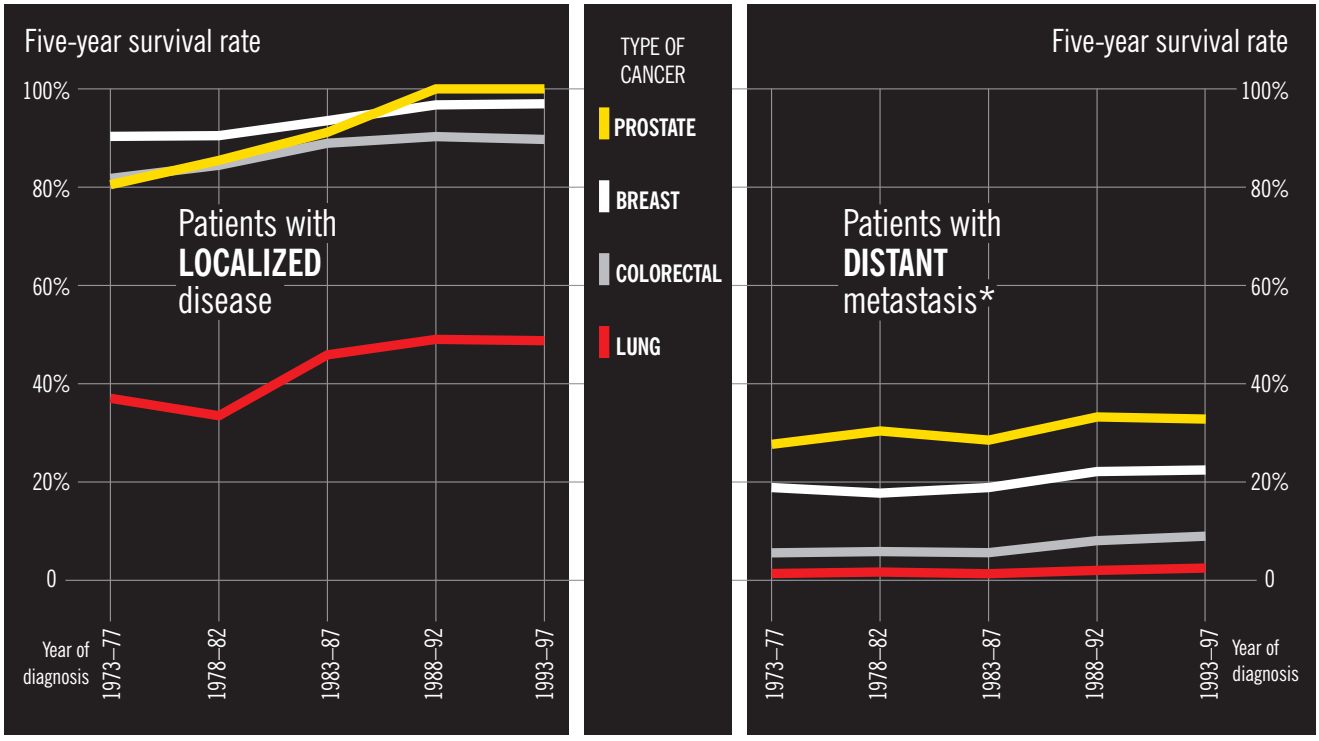
On the other side was Sidney Farber, the Boston physician known as the godfather of cancer research. He wanted public backing for a massive, coordinated assault. "We cannot wait for full understanding; the 325,000 patients with cancer who are going to die this year cannot wait; nor is it necessary, in order to make great progress in the cure of cancer, for us to have the full solution of all the problems of basic research," Farber testified in congressional hearings that fall. "The history of medicine is replete with examples of cures obtained years, decades, and even centuries before the mechanism of action was understood for these cures—from vaccination, to digitalis, to aspirin."

Farber lost.

Today the cancer effort is utterly fragmented—so much so that it's nearly impossible to track down where the money to pay for

CANCER'S BIG FOUR KILLERS

In 1971, when the war on cancer began, 50% of people diagnosed with the disease went on to live at least five years. Today, 33 years and some $200 billion later, the five-year survival rate is 63%, a modest 13-point gain. But a look behind the numbers for the four biggest killers—lung, colon and rectal, breast, and prostate cancer—reveals that progress isn't being made where you might think it is. With the help of early detection and treatment, more patients are living longer. Once a cancer has spread, however, chances of survival are scarcely better now than they were three decades ago.



FORTUNE CHARTS / SOURCE: SURVEILLANCE, EPIDEMIOLOGY AND END RESULTS (SEER)

*Cancer that has spread beyond the primary site region.

all this research is coming from. But let's try anyway.

We begin with the NCI budget. Set by Congress, this year's outlay for fighting cancer is $4.74 billion. Critics have complained that is a mere 3.3% over last year's budget, but Uncle Sam gives prodigiously in other ways too—a fact few seem to realize. The NIH, technically the NCI's parent, will provide an additional $909 million this year for cancer research through the National Institute of Environmental Health Sciences and other little-noticed grant mechanisms. The Department of Veterans Affairs will likely spend just over the $457 million it spent in 2003 for research and prevention programs. The CDC will chip in around $314 million for outreach and education. Even the Pentagon pays for cancer research—offering $249 million this year for nearly 500 peer-reviewed grants to study breast, prostate, and ovarian cancer.

Now throw state treasuries into the mix—governors signed 89 cancer-related appropriations from 1997 to 2003—plus the fundraising muscle of cancer charities, cancer centers, and research hospitals, which together will raise some $2 billion this year from generous donors, based on recent tax forms. And finally, that huge spender Big Pharma. The Tufts Center for the Study of Drug Development estimates that drug companies will devote about $7.4 billion, or roughly a quarter of their annual R&D spending, to products for cancer and metabolic and endocrine diseases.

When you add it all up, Americans have spent, through taxes, donations, and private R&D, close to $200 billion, in inflation-adjusted dollars, since 1971. What has that national investment netted so far?

Without question, the money has bought us an enormous amount of knowledge, just as Varmus says. Researchers have mapped the human cell's intricate inner circuitry in extraordinary detail, identifying dozens of molecular chains of communication, or "signaling pathways," among various proteins, phosphates, and lipids made by the body. In short, scientists now know (or think they know) nearly all the biochemical steps that a healthy cell uses to multiply, to shut down its growth, and to sense internal damage and die at the right time—as well as many of the genes that encode for these processes. What's more, by extension, they know how these same gene-induced mechanisms go haywire in a cancer cell.

According to PubMed, the NCI's online database, the cancer research community has published 1.56 million papers—that's right: 1.56 million!—largely on this circuitry and its related genes in hundreds of journals over the years. Many of the findings are shared at the 100-plus international congresses, symposiums, and conventions held each year.

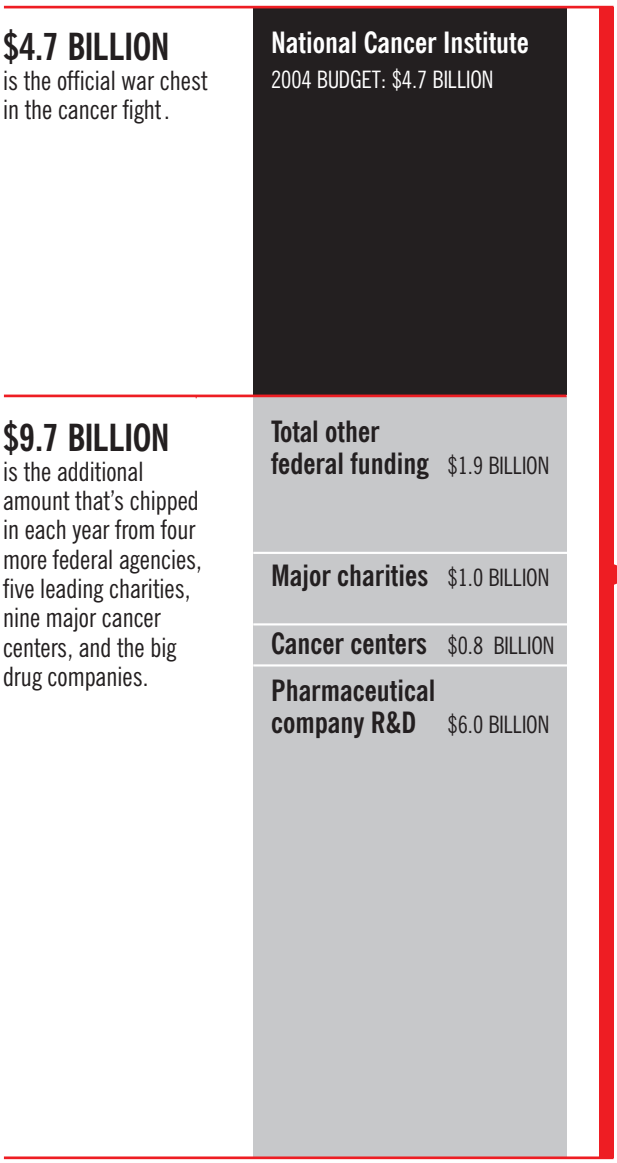
Yet somehow, along the way, something important has gotten lost. The search for knowledge has become an end unto itself rather than the means to an end. And the research has become increasingly narrow, so much so that physician-scientists who want to think systemically about cancer or the organism as a whole—or who might have completely new approaches—often can't get funding.

Take, for instance, the NCI's chief funding mechanism, something called an RO1 grant. The grants are generous, averaging $338,000

apiece in 2003. And they are one of the easiest sweepstakes to win: One in three applications is accepted. But the money goes almost entirely to researchers who focus on very specific genetic or molecular mechanisms within the cancer cell or other tissue. The narrower the research niche, it sometimes seems, the greater the rewards the researcher is likely to attain. "The incentives are not aligned with the goals," says Leonard Zwelling, vice president for research administration at M.D. Anderson, voicing the feeling of many. "If the goal is to cure cancer, you don't incentivize people to have little publications."

FUNDING APLENTY

The National Cancer Institute isn't the half of it. Major bucks for cancer R&D come from many sources—some you'd never expect (like the Pentagon).



FORTUNE CHART / SOURCES: Totals derive from data for the most recent year available. Other federal funding includes cancer spending by NIH (except NCI) and the VA (excluding treatment), CDC, and Pentagon. Data on charities and cancer centers are from federal tax forms; state figures are not included. Pharma total is from Tufts Center for the Study of Drug Development and *Fortune* estimates.

Jean-Pierre Issa, a colleague of Zwelling's who studies leukemias, is equally frustrated by the community's mindset. Still, he admits, the system's lure is powerful. "You get a paper where you change one gene ever so slightly and you have a drastic effect of cancer in the mouse, and that paper gets published in *Science* or *Nature*, and in your best journals. That makes your reputation. Then you start getting grants based on that," he says. "Open any major journal and 80% of it is mice or drosophila [fruit flies] or nematodes [worms]. When do you get human studies in there?"

Indeed, the cancer community has published an extraordinary 150,855 experimental studies on mice, according to a search of the PubMed database. Guess how many of them have led to treatments for cancer? Very, very few. In fact, if you want to understand where the War on Cancer has gone wrong, the mouse is a pretty good place to start.

THE MODELS OF CANCER STINK

OUTSIDE ERIC LANDER'S OFFICE is a narrow, six-foot-high poster. It is an org chart of sorts, a taxonomy, with black lines connecting animal species. The poster's lessons feel almost biblical—it shows, for example, that the zebrafish has much in common with the chicken; that hedgehog and shrew are practically kissing cousins; and that while a human might look more like a macaque than a platypus or a mouse, it ain't that big of a leap, really.

The connection, of course, is DNA. Our genomes share much of the same wondrous code of life. And therein lie both the temptation and the frustration inherent in cancer research today. Certain mutated genes cause cells to proliferate uncontrollably, to spread to new tissues where they don't belong, and to refuse to end their lives when they should. That's cancer. So research, as we've said, now revolves around finding first, the molecular mechanisms to which these mutated genes give rise, and second, drugs that can stop them.

The strategy sounds obvious—and nobody makes it sound more so than Lander, the charismatic founding director of the Whitehead Institute's Center for Genome Research in Cambridge, Mass., and a leader of the Human Genome Project. The "Prince of Nucleotides," as FORTUNE once called him, sketches the biological route to cancer cures as if he were directing you to the nearest Starbucks: "There are only, pick a number, say, 30,000 genes. They do only a finite number of things. There are only a finite number of mechanisms that cancers have. It's a large number; when I say finite, I don't mean to trivialize it. There may be 100 mechanisms that cancers are using, but 100 is only 100."

So, he continues, we need to orchestrate an attack that isolates these mechanisms by knocking out cancer-promoting genes one by one in mice, then test drugs that kill the mutant cells. "These are doable experiments," he says. "Cancers by virtue of having mutations also acquire Achilles' heels. Rational cancer therapies are about finding the Achilles' heel associated with each new mutation in a cancer."

The principle is, in all likelihood, dead-on. The process itself, on the other hand, has one heck of an Achilles' heel. And that takes us back to the six-foot poster showing the taxonomy of genomes. A mouse gene may be very similar to a human gene, but the rest of the mouse is very different.

The fact that so many cancer researchers seem to forget or ignore this observation when working with "mouse models" in the lab clearly irks Robert Weinberg. A professor of biology at MIT and winner of the National Medal of Science for his discovery of both the first human oncogene and the first tumor-suppressor gene, Weinberg is as no-nonsense as Lander is avuncular. Small and mustachioed, with Hobbit-like fingers, he plops into a brown leather La-Z-Boy that is somehow wedged into the middle of his cramped office, and launches into a lecture:

"One of the most frequently used experimental models of human cancer is to take human cancer cells that are grown in a petri dish, put them in a mouse—in an immunocompromised mouse—allow them to form a tumor, and then expose the resulting xenograft to different kinds of drugs that might be useful in treating people. These are called preclinical models," Weinberg explains. "And it's been well known for more than a decade, maybe two decades, that many of these preclinical human cancer models have very little predictive power in terms of how actual human beings—actual human tumors inside patients—will respond." Despite the genetic and organ-system similarities between a nude mouse and a man in a hospital gown, he says, the two species have key differences in physiology, tissue architecture, metabolic rate, immune system function, molecular signaling, you name it. So the tumors that arise in each, with the same flip of a genetic switch, are vastly different.

Says Weinberg: "A fundamental problem which remains to be solved in the whole cancer research effort, in terms of therapies, is that the preclinical models of human cancer, in large part, *stink*."

A few miles away, Bruce Chabner also finds the models lacking. A professor of medicine at Harvard and clinical director at the Massachusetts General Hospital Cancer Center, he explains that for a variety of biological reasons the "instant tumors" that researchers cause in mice simply can't mimic human cancer's most critical and maddening trait, its quick-changing DNA. That characteristic, as we've said, leads to staggering complexity in the most deadly tumors.

"If you find a compound that cures hypertension in a mouse, it's going to work in people. We don't know how toxic it will be, but it will probably work," says Chabner, who for many years ran the cancer-treatment division at the NCI. So researchers routinely try the same approach with cancer, "knocking out" (neutralizing) this gene or knocking in that one in a mouse and causing a tumor to appear. "Then they say, 'I've got a model for lung cancer!' Well, it ain't a model for lung cancer, because lung cancer in humans has a hundred mutations," he says. "It looks like the most complicated thing you've ever seen, genetically."

Homer Pearce, who once ran cancer research and clinical investigation at Eli Lilly and is now research fellow at the drug company, agrees that mouse models are "woefully inadequate" for determining whether a drug will work in humans. "If you look at the millions and millions and millions of mice that have been cured, and you compare that to the relative success, or lack thereof, that we've achieved in the treatment of metastatic disease clinically," he says, "you realize that there just has to be something wrong with those models."

Vishva Dixit, a vice president for research in molecular oncology at Genentech in South San Francisco, is even more horrified that "99% of investigators in industry and in academia use xenografts." Why is the mouse model so heavily used? Simple. "It is very convenient, easily manipulated," Dixit explains. "You can assess tumor size just by looking at it."

Although drug companies clearly recognize the problem, they haven't fixed it. And they'd better, says Weinberg, "if for no other reason than [that] hundreds of millions of dollars are being wasted every year by drug companies using these models."

Even more depressing is the very real possibility that reliance on this flawed model has caused researchers to pass over drugs that *would* work in humans. After all, if so many promising drugs that clobbered mouse cancers failed in man, the reverse is also likely: More than a few of the hundreds of thousands of compounds discarded over the past 20 years might have been truly effective agents. Roy Herbst, who divides his time between bench and bedside at M.D. Anderson and who has run big trials on Iressa and other targeted therapies for lung cancer, is sure that happens often. "It's something that bothers me a lot," he says. "We probably lose a lot of things that either don't have activity on their own, or we haven't tried in the right setting, or you don't identify the right target."

If everyone understands there's a problem, why isn't anything being done? Two reasons, says Weinberg. First, there's no other model with which to replace that poor mouse. Second, he says, "is that the FDA has created inertia because it continues to recognize these [models] as the gold standard for predicting the utility of drugs."

"People obsessed with cures, cures, cures are being—I hate to use the word—selfish by ignoring what could be done in terms of prevention."

"WE HAVE A SHORTAGE OF GOOD IDEAS"

IT IS ONE OF THE MANY chicken-and-egg questions bedeviling the cancer culture. Which came first: the FDA's imperfect standards for judging drugs or the pharmaceutical companies' imperfect models for testing them?

The riddle is applicable not just to early drug development, in which flawed animal models fool bench scientists into thinking their new compounds will wallop tumors in humans. It comes up, with far more important ramifications, in the last stage of human testing, when the FDA is looking for signs that a new drug is actually helping the patients who are taking it. In this case, the faulty model is called tumor regression.

It is exciting to see a tumor shrink in mouse or man and know that a drug is doing that. A shrinking tumor is intuitively a good thing. So it is no surprise that it's one of the key endpoints, or goals, in most clinical trials. That's in no small part because it is a *measurable* goal: We can see it happening. (When you read the word "response" in a newspaper story about some exciting new cancer drug, tumor shrinkage is what it's talking about.)

But like the mouse, tumor regression by itself is actually a lousy predictor for the progression of disease. Oncologists can often shrink a tumor with chemo and radiotherapy. That sometimes makes the cancer easier to remove surgically. If not, it still may buy a little time. However, if the doctors don't get every rotten cell, the sad truth is that the regression is not likely to improve the person's chances of survival.

That's because when most malignant solid tumors are diagnosed, they are typically quite large already—the size of a grape, perhaps, with more than a billion cells in the tumor mass. By the time it's discovered, there is a strong chance that some of those cells have already broken off from the initial tumor and are on their way to another part of the body. This is called metastasis.

Most of those cells will not take root in another tissue or organ: A metastasizing cell has a very uphill battle to survive once it enters the violent churn of the bloodstream. But the process has begun—and with a billion cells dividing like there's no tomorrow, an ever-growing number of metastases will try to make the journey. Inevitably, some will succeed.

In the end, it is not localized tumors that kill people with cancer; it is the process of metastasis—an incredible *90% of the time*. Aggressive cells spread to the bones, liver, lungs, brain, or other vital areas, wreaking havoc.

So you'd think that cancer researchers would have been bearing down on this insidious phenomenon for years, intently studying the intricate mechanisms of invasion. Hardly. According to a FORTUNE examination of NCI grants going back to 1972, less than 0.5% of study proposals focused primarily on metastasis—trying to understand, for instance, its role in a specific cancer (e.g., breast, prostate) or just the process itself. Of nearly 8,900 NCI grant proposals awarded last year, 92% didn't even *mention* the word metastasis.

One accomplished researcher sent an elegant proposal into the NCI two years ago to study the epigenetics (changes in normal gene function) of metastases vs. primary tumors. It's now in its third resubmission, he says. "I mean, there is nothing known about that. But somehow I can't interest people in funding this!"

M.D. Anderson's Josh Fidler suggests that metastasis is getting short shrift simply because "it's tough. Okay? And individuals are not rewarded for doing tough things." Grant reviewers, he adds, "are more comfortable with the focused. Here's an antibody I will use, and here's blah-blah-blah-blah, and then I get the money."

Metastasis, on the other hand, is a big idea—an organism-wide phenomenon that may involve dozens of processes. It's hard to do replicable experiments when there are that many variables. But that's the kind of research we *need*. Instead, says Weinberg, researchers opt for more straightforward experiments that generate plenty of reproducible results. Unfortunately, he says,"the accumulation of data gives people the illusion they've done something meaningful."

That drive to accumulate data also goes to the heart of the regulatory process for drug development. The FDA's mandate is to make sure that a drug is safe and that it works before allowing its sale to the public. Thus, the regulators need to see hard data showing that a drug has had some effect in testing. However, it's hard to see "activity" in preventing something from happening in the first place. There are probably good biomarkers—proteins, perhaps, circulating in the body—that can tell us that cancer cells have begun the process of spreading to other tissues. As of yet, though, we don't know what they are.

So pharma companies, quite naturally, don't concentrate on solving the problem of metastasis (the thing that kills people); they focus on devising drugs that shrink tumors (the things that don't).

Dozens of these drugs get approved anyway. At the same time, many don't—and the FDA is invariably blamed for holding up the War on Cancer. The fault, however, is less the umpire's than the players'. That's because many tumor-shrinking drugs simply don't perform much better than the standard treatments. Or as Rick Pazdur, director of oncology drugs for the FDA, puts it, "It's efficacy, stupid! One of the major problems that we have is dealing with this meager degree of efficacy." When it's clear that something is working, the agency is generally quick to give it priority review and/or accelerated approval, two mechanisms that speed up the regulatory process for compounds aimed at life-threatening diseases. "We have a shortage of good ideas that are likely to work," agrees Bruce Johnson, a Dana-Farber oncologist who runs lung-cancer research for institutions affiliated with the Harvard Medical School, a huge partnership that includes Massachusetts General Hospital, Brigham and Women's Cancer Center, and others.

That is also the devastating conclusion of a major study published last August in the *British Medical Journal*. Two Italian pharmacologists pored over the results of trials of 12 new anticancer drugs that had been approved for the European market from 1995 to 2000, and compared them with standard treatments for their respective diseases. The researchers could find no substantial advantages—no improved survival, no better quality of life, no added safety—with any of the new agents. All of them, though, were several times more expensive than the old drugs. In one case, the price was 350 times higher.

WHY THE NEW DRUGS DISAPPOINT

FLAWED MODELS FOR DRUG development. Obsession with tumor shrinkage. Focus on individual cellular mechanisms to the near exclusion of what's happening in the organism as a whole. All these failures come to a head in the clinical trial—a rigidly controlled, three-phase system for testing new drugs and other medical procedures in humans. The process remains the only way to get from research to drug approval—and yet it is hard to find *anyone* in the cancer community who isn't maddeningly frustrated by it.

In February 2003 a blue-ribbon panel of cancer-center directors concluded that clinical trials are "long, arduous," and burdened with regulation; without major change and better resources, the panel concluded, the "system is likely to remain inefficient, unresponsive, and unduly expensive."

All that patients know is that the process has little to offer them. Witness the fact that a stunning *97%* of adults with cancer don't bother to participate.

There are two major problems with clinical trials. The first is that their duration and cost mean that drug companies—which sponsor the vast majority of such trials—have an overwhelming incentive to test compounds that are likely to win FDA approval. After all, they are public companies by and large, with shareholders demanding a return on investment. So the companies focus not on breakthrough treatments but on incremental improvements to existing classes of drugs. The process does not encourage risk taking or entrepreneurial approaches to drug discovery. It does not encourage brave new thinking. Not when a drug typically takes 12 to 14 years to develop. And not with $802 million—that's the oft-cited cost of developing a drug—on the line.

What's more, the system essentially forces companies to test the

most promising new compounds on the sickest patients—where it is easier to see some activity (like shrinking tumors) but almost impossible to cure people. At that point the disease has typically spread too far and the tumors have become too ridden with genetic mutations. Thus drugs that might have worked well in earlier-stage patients often never get the chance to prove it. (As you'll see, that may be a huge factor in the disappointing response so far of one class of promising new drugs.)

The second problem is even bigger: Clinical trials are focused on the wrong goal—on doing "proper" science rather than saving lives. It is not that they provide bad care—patients in trials are treated especially well. But the trials' very reason for being is to test a hypothesis: Is treatment X better than treatment Y? And sometimes—too often, sadly—the information generated by this tortuously long process doesn't much matter. If you've spent ten-plus years to discover that a new drug shrinks a tumor by an average of 10% more than the existing standard of care, how many people have you really helped?

Take two drugs approved in February for cancer of the colon and rectum: Erbitux and Avastin. In each case it took many months just to enroll the necessary number of patients in clinical trials. Participating doctors then had to administer the drugs according to often arduous preset protocols, collecting reams of data along the way. (ImClone's well-known troubles with the FDA occurred because it had not set up its trials properly.)

And here's what clinicians learned after years of testing. When Avastin was added to the standard chemotherapy regimen, the combination managed to extend the lives of some 400 patients with terminal colorectal cancer by a median 4.7 months. (A previous trial of the drug on breast cancer patients failed.) Oncologists consider the gain substantial, considering that those in advanced stages of the disease typically live less than 16 months.

And Erbitux? Although it did indeed shrink tumors, *it has not been shown to prolong patients' lives at all*. Some certainly have fared well on the drug, but survival on average for the groups studied didn't change. Still, Erbitux was approved for use primarily in "third line" therapy, after every other accepted treatment has failed. A weekly dose costs $2,400.

Remember, it took several years and the participation of thousands of patients in three stages of testing, tons of data, and huge expense to find out what the clinicians and researchers already knew in the earliest stage of human testing: Neither drug will save more than a handful of the 57,000 people who will die of colorectal cancer this year.

You could say the same for AstraZeneca's Iressa, another in the new class of biological wonder drugs—compounds specifically "targeted" to disrupt the molecular signals in a cancer cell. Not a single controlled trial has shown Iressa to have a major patient benefit such as the easing of symptoms or improved survival—a fact that the company's upbeat press releases admit as if it were legal boilerplate. Even so, the FDA okayed the pill last year for last-ditch use against a type of lung cancer, citing the fact that it had shrunk tumors in 10% of patients studied.

"Very smart people, with a lot of money, have done trials of over 10,000 patients around the world—testing these new molecular targeted drugs," says Dana-Farber's Bruce Johnson. "AstraZeneca tested Iressa. Isis Pharmaceuticals and Eli Lilly tested a compound called Isis 3521. Several different companies ended up investing tens of millions of dollars, and all came up with a big goose egg."

The one targeted drug that clearly isn't a goose egg is Novartis's Gleevec, which has been shown to save lives as well as stifle tumors. The drug has a dramatic effect on an uncommon kind of leukemia called CML and an even more rare stomach cancer named GIST. Early reports say it also seems to work, in varying degrees, in up to three other cancers. Gleevec's success has been held out as the "proof of principle" that the strategy we've followed in the War on Cancer all these years has been right.

But not even Gleevec is what it seems. CML is not a complicated cancer: In it, a single gene mutation causes a critical signaling mechanism to go awry; Gleevec ingeniously interrupts that deadly signal. Most common cancers have perhaps as many as five to ten different things going wrong. Second, even "simple" cancers get smarter: The malignant cells long exposed to the drug (which must be taken forever) mutate their way around the molecular signal that Gleevec blocks, building drug resistance.

No wonder cancer is so much more vexing than heart disease. "You don't get multiple swings," says Bob Cohen, senior director for commercial diagnostics at Genentech. Use a drug that does not destroy the tumor completely and "the heterogeneity will evolve from the [surviving] cells and say, 'I don't give a rat's ass! You can't screw me up with this stuff.' Suddenly you're squaring and cubing the complexity. That's where we are." And that's why the only chance is to attack the disease earlier—and on multiple fronts.

Three drugs, four drugs, five drugs in combination. Cocktails of experimental compounds, of course, were what doctors used to control HIV, whose rapidly mutating virus was once thought to be a death sentence. Virtually every clinician and scientist interviewed for this story believes a similar approach is needed with the new generation of anticancer drugs. But once again, institutional forces within the cancer world make it nearly impossible.

"If you look at the millions of mice that have been cured of cancer, and compare it to humans, you realize there just has to be something wrong with those models."

Combining unapproved drugs in clinical trials brings up a slew of legal and regulatory issues that cause pharma companies to squirm. While many drug-company oncologists are as committed to the public's well-being as government or cancer-center researchers, they have less flexibility to take chances on an idea. Ultimately, they need FDA approval for their investigational compounds. If two or three unapproved drugs are tested in concert, it's even harder to figure out what's working and what isn't, and whether one drug is responsible for side-effects or the combination. "It becomes much more challenging in the context of managing the databases, interpreting the results, and owning the data," adds Lilly's Pearce.

Over dinner at Ouisie's Table in Houston, M.D. Anderson's Len Zwelling, who oversees regulatory compliance for the center's

800-plus clinical trials, and his wife, Genie Kleinerman, who is chief of pediatrics there, have no trouble venting about the legal barriers that seem to be growing out of control. It takes no more than ten minutes for Kleinerman to rattle off three stories about trying to bring together different drug companies in clinical trials for kids with cancer. In the first attempt, the trial took so long that the biotech startup with the promising agent went out of business. In the second the lawyers haggled over liability concerns until both companies pulled out. The third, however, was the worst. There were two drugs that together seemed to jolt the immune system into doing a better job of targeting malignant cells of osteosarcoma, a bone cancer that occurs in children. "Working with the lawyers, it was just impossible," she says, "because each side wanted to own the *rights* to the combination!"

CHANGING THE WAY WE THINK ABOUT CANCER

STRANGE AS IT MAY SEEM, much of our failure in fighting cancer—and more important, much of the potential for finally winning this fight—has to do with a definition. Some 2,400 years ago the Greek physician Hippocrates described cancer as a disease that spread out and grabbed on to another part of the body like "the arms of a crab," as he elegantly put it. Similarly, medical textbooks today say cancer begins when the cells of an expanding tumor push through the thin protein "basement" membrane that separates them from another tissue. It's a fancy way of saying that to be cancer, a malignant cell has to invade another part of the body.

Michael Sporn, a professor of pharmacology and medicine at Dartmouth Medical School, has two words for this: "Absolute nonsense!" He goes on: "We've been stuck with this definition of what cancer is from 1890. It's what I was taught in medical school: 'It's not cancer until there's invasion.' That's like saying the barn isn't on fire until there are bright red flames coming out of the roof."

In fact, cancer begins much earlier than that. And therein lies the best strategy to contain it, believes Sporn, who was recently named an Eminent Scholar by the NCI: Let's aggressively find those embers that have been smoldering in many of us for years—and douse them before they become a full-fledged blaze. Prevent cancer from ever entering that deadly stage of malignancy in the first place.

Sporn, who spent more than three decades at the NCI, has been struggling for many years to get fellow researchers to start thinking about cancer not as a state of being (that is, an invasive group of fast-growing cells) but as a *process*, called carcinogenesis. Cancer, as Sporn tells it, is a multistage disease that goes through various cell transformations and sometimes long periods of latency in its progression.

Thus, the trick is to intervene earlier in that process—especially at key points when lesions occur (known to doctors as dysplasias, hyperplasias, and other precancerous cell phases). To do that, the medical community has to break away from the notion that people in an early stage of carcinogenesis are "healthy" and therefore shouldn't be treated. People are not healthy if they're on a path toward cancer.

If this seems radical and far-fetched, consider: We've prevented millions of heart attacks and strokes by using the very same strategy. Sporn likes to point out that heart disease doesn't start with the heart attack; it starts way earlier with the elevated blood cholesterol and lipids that cause arterial plaque. So we treat those. Stroke doesn't start with the blood clot in the brain. It starts with hypertension. So we treat it with both lifestyle changes and drugs. "Cardiovascular disease, of course, is nowhere near as complex as cancer is," he says, "but the principle is the same." Adds Sporn: "All these people who are obsessed with cures, cures, cures, and the miraculous cure which is still eluding us, they're being—I hate to use this word, but if you want to look at it pragmatically—they're being selfish by ignoring what could be done in terms of prevention."

The amazing thing about this theory—other than how obvious it is—is that we can start applying it *right now*. Precancerous cell changes mark the progression to many types of solid-tumor cancers; many such changes are relatively easy to find and remove, and others are potentially reversible with current drugs and other treatments.

A perfect example is the Pap smear, which detects premalignant changes in the cells of the cervix. That simple procedure, followed by the surgical removal of any lesions, has dropped the incidence and death rates from cervical cancer by 78% and 79%, respectively, since the practice began in the 1950s. In countries where Pap smears aren't done, cervical cancer is a leading killer of women.

Same goes for colon cancer. Not every adenomatous polyp in the colon (a lesion in the organ's lining) goes on to become malignant and invasive. But colon cancers have to go through this abnormal step on their way to becoming deadly. The list of other dysplasia-like conditions goes on and on, from Barrett's esophagus (a precursor to cancer there) to hyperkeratosis (head and neck cancers). Obviously, doctors are already doing this kind of testing with some cancers, but they need to do it much, much more.

Some complain that the telltale biomarkers of carcinogenesis, while getting more predictive, still are far from definitive, and that we should wait until we know more. (Sound familiar?) Researchers in heart disease, meanwhile, have taken an opposite tack and been far more successful. Neither high cholesterol nor hypertension guarantees future cardiovascular disease, but they're treated anyway.

A few cancer researchers have made great strides in finding more early warning signs—looking for protein "signatures" in blood, urine, or even skin swabs that can identify precancerous conditions and very early cancers that are likely to progress. For instance, Lance Liotta, chief of pathology at the NCI, has demonstrated that ovarian cancer can be detected by a high-tech blood test—one that identifies a unique "cluster pattern" of some 70 different proteins in a woman's blood. "We've discovered a previously unknown ocean of markers," he says. And it's potentially a mammoth lifesaver. With current drugs, early-stage ovarian cancer is more than 90% curable; late stage is 75% deadly. Early results on a protein test for pancreatic cancer are promising as well, says Liotta.

Yes, the strategy has costs. Some say wholesale testing of biomarkers and early lesions—many of which won't go on to become invasive cancers—would result in a huge burden for the healthcare system and lead to a wave of potentially dangerous surgeries to remove things that might never become lethal anyway. But surely the costs of not acting are much greater.

Indeed, it is an encouraging sign that Andy von Eschenbach, director of the NCI, and Elias Zerhouni, who leads the NIH, are both believers in this strategy. "What our investment in biomedical research has led us to is understanding cancer as a disease process and the various steps and stages along that pathway—from being very susceptible to it, to the point where you get it, and ultimately suffer and die from it," says von Eschenbach, a former urologist who

has survived prostate and a pair of skin cancers. So, he says, he wants to lead the NCI on a "mission to prevent the process from occurring in the first place or detect the occurrence of cancer early enough to eliminate it with less morbidity."

HOW TO WIN THE WAR

THERE HAS BEEN TALK like this before. But the money to fund the assault never came. And several cancer experts interviewed for this story worry that the new rhetoric from the NCI, while encouraging, has yet to move beyond lip service.

For the nation finally to turn the tide in this brutal war, the cancer community must embrace a coordinated assault on this disease. Doctors and scientists now have enough knowledge to do what Sydney Farber hoped they might do 33 years ago: to work as an army, not as individuals fighting on their own.

The NCI can begin this transformation right away by drastically changing the way it funds research. It can undo the culture created by the RO1s (the grants that launched a million me-too mouse experiments) by shifting the balance of financing to favor cooperative projects focused on the big picture. The cancer agency already has such funding in place, for endeavors called SPOREs (short for specialized programs of research excellence). These bring together researchers from different disciplines to solve aspects of the cancer puzzle. Even so, funding for individual study awards accounts for a full quarter of the agency's budget and is more than 12 times the money spent on SPORE grants. The agency needs to stop being an automatic teller machine for basic science and instead use the taxpayers' money to marshall a broad assault on this elusive killer—from figuring out how to stop metastasis in its tracks to coming up with testing models that better mimic human response.

At the same time, the NCI should commit itself to finding biomarkers that are predictive of cancer development and that, with a simple blood or urine test (like PSA) or an improved molecular imaging technique (PET and CT scans), can give patients a chance to preempt or control the disease. For that matter, as a nation we could prevent tens of thousands of cancers—and 30% of all cancer deaths, according to the NCI—by getting people to stop smoking. This all-too-obvious observation was made by every researcher I interviewed.

Alas, this is not a million-dollar commitment. It's a billion-dollar one. But the nation is already investing billions in research, and that doesn't even include the $64 billion a year we spend on treatment. To make the resource shift easier, Congress should move the entire federal war chest for cancer into one bureaucracy, not five. Cancer research should be managed by the NCI, not the VA and Pentagon.

Just as important, the cancer leadership, the FDA, and lawmakers need to transform drug testing and approval into a process that delivers information on what's working and what's not to the patients far faster. If the best hope to treat most cancer lies in using combinations of drugs, we're going to have to remove legal constraints and give drug companies incentives to test investigational compounds together in shorter trials. Those should be funded by the NCI—in a process that's distinct from individual drug approval. One bonus for the companies: If joint activity showed marked improvement in survival, the FDA process could be jump-started. *continued*

"It's going to require a community conversation to facilitate this change," says Eli Lilly's Homer Pearce. "I think everyone believes that at the end of the day, cancer is going to be treated with multi-

MIRACLE CURES THAT WEREN'T

Decades of breakthroughs have raised hopes again and again for people with cancer—but have failed to deliver on expectations.

Radiation therapy Soon after Wilhelm Roentgen's discovery of X-rays in 1895, some doctors predicted that the high-energy waves from exotic "cyclotrons" could be used to kill most cancerous tumors. A century-plus later, targeted radiation is a critical weapon in the oncologist's arsenal but not the magic bullet many thought.

Interferon In 1980, the world was afrenzy about the big "IF"—an immune-system booster produced by the body in tiny quantities—as word spread that this natural virus fighter could also shrink tumors. Though still in use in some cancer therapies, IF has not fulfilled its early promise.

Interleukin-2 Like Interferon, this protein helps activate the body's immune system. And like IF, IL-2 was once thought to be the "cancer breakthrough" we were waiting for (see FORTUNE's 1985 cover, lower right). But after years of testing and tweaking, the therapy has led to only scattered remissions in patients.

Endostatin After a flurry of early hype, this first of many compounds designed to fight tumor angiogenesis failed dramatically in human tests. The jury is still out on its next-generation kin.

Gleevec The little yellow pill from Novartis has wondrous effect in a few rare cancers involving simple mutations, although the disease can grow resistant to this "targeted" biological drug.

ple targeted agents—maybe in combination with traditional chemotherapy drugs, maybe not. Because that's where the biology is leading us, it's a future that we have to embrace—though it will definitely require different models of cooperation."

When clinical trials begin to offer patients more than incremental improvements over existing drug treatments, people with cancer will rush into the studies. And when participation rates go up, it will accelerate the process so that we can test more combinations faster and cheaper.

To see which drugs truly have promise, however, we need to do one thing more: test them on people in less advanced stages of disease. The reason, once again, comes back to cancer's genetic instability—a progression that not only ravages the body but also riddles tumors with mutations. When cancer patients are in the end stage of the disease, drugs that might have a potent effect on newer cancers fail to show much progress at all. Our current crop of rules, however, pushes drug companies into this can't-win situation, where the only way out is incremental improvements to existing therapies. Drugs that might well help some cancer patients are now getting tossed by the wayside because they don't help people whom they couldn't have helped in any case. This has to stop.

"It's like a Greek tragedy," says Intel's Andy Grove. "Everybody plays his part, everybody does what's right by his own life, and the total just doesn't work."

Witness what has happened with the new class of drugs developed to fight the process called angiogenesis ("angio" refers to blood vessels, and "genesis" to new growth)—compounds designed to block the development of capillaries that supply oxygen and nutrients to tumors. Avastin is the best known, but there are some 40 anti-angiogenesis drugs in clinical trials.

This, by the way, is one of those big ideas that the cancer culture didn't take seriously, and would barely fund, for decades. The concept was pioneered 43 years ago by Judah Folkman, now a surgeon at Children's Hospital Boston. While studying artificial blood in a Navy lab, he was struck by a simple and seemingly obvious idea: Every cell needs oxygen to grow, including cancer cells. Since oxygen in the body comes from blood, fast-growing tumors couldn't develop without access to blood vessels.

Folkman later figured out that tumors actually recruited new blood vessels by sending out a protein signal. If you could turn off that growth signal, he reasoned, you could starve the tumors and keep them tiny. The surgeon submitted a paper on his experiments to various medical journals, but the article was rejected time and again. That is, until an editor at the *New England Journal of Medicine* heard Folkman give a lecture and offered to publish it in the *Journal's* Beth Israel Hospital Seminars in 1971—ironically, the year the War on Cancer began.

After decades of resistance, the cancer culture has finally come around to Folkman's thinking—as the reception greeting Avastin makes clear. Still, the biggest promise of anti-angiogenesis drugs will be realized only when doctors can use them to treat earlier-stage patients. That's because the drugs designed to choke the tumor's blood supply often take a far longer time to work than traditional toxic chemo—time that people with advanced disease and fast-growing cancers may not have. Doctors also need the freedom to administer such drugs in combination. Tumors recruit blood vessels through several signaling mechanisms, researchers believe, so the best approach is to apply several drugs, cutting off all routes.

Who knows? A new paradigm in treatment may emerge from Folkman's 40-year-old idea. Yet to make this simple and seemingly obvious shift, the entire cancer culture must change—from the rules governing drug approval to tort law and intellectual property rights. Science now has the knowledge and the tools; we need to act.

THE GOOD DOCTOR

IN THE WEEKS SINCE I finished my reporting and began writing this story, one image has stuck with me: a drawerful of letters. The letters belong to Eric Winer, a 47-year-old physician at Dana-Farber. He and I had been talking for close to an hour when he showed me the drawer.

It was late on a Friday evening, and Winer, still in the clinic, was describing the progress we were making in this war, his reedy voice cracking higher every so often. He was telling me of his optimism. That's when he mentioned the drawer: "That enthusiasm is very much tempered by the fact that we have 40,000 women dying of breast cancer every year. Um, and you know, I've got a file full of letters that are almost entirely from family members of my patients who died…."

I asked to see it, and then asked again, and there it was, in the bottom drawer of his filing cabinet—two overstuffed folders of mostly handwritten notes. Once the letters go in, Winer confessed, he never looks at them again. "I don't go back," he said sheepishly. "My excuse initially was that if anyone wanted to say I was a bad doctor, I'd hold on to these things that people said about me. And I could prove that I wasn't."

If the walls of his office are any indication, there is no way Winer is a bad doctor. They are covered with loving mementos from patients. There is a picture of Tolstoy from a woman whose breast tumors were initially shrunk by Herceptin, but who died within five years. (Winer had once mentioned to her to that he had majored in Russian history at Yale.) There's a photo of the Grand Canyon taken by a young nurse who was determined to take a trip out West with her 10-year-old son before she died. The daughter of another patient even cornered Lance Armstrong and begged him to sign a neon-yellow jersey for Winer, who is an avid cyclist. It is the most prominent thing in his office.

No, it isn't just the patients in this War on Cancer who need renewed hope. It is the foot soldiers as well. F

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