

# Chance and the prepared mind in drug discovery

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Chance and accidents play important roles in scientific discoveries, but they are not blind luck. Serendipity is not merely stumbling on things unsought for, it is the ability to see significances and find values in the things stumbled upon. Without this ability, accidents do not lead to discoveries, as Pasteur observed: “Chance favors the prepared mind.” What are the characteristics of a prepared mind in science? How do chance and serendipity work in scientific research in general and drug discovery in particular?

## At the frontier of knowledge

It would not become a drug for heart diseases, researchers at Pfizer sighed. For years they worked on sildenafil, an inhibitor of the PDE5 enzyme, which they hoped would be effective in relaxing coronary arteries and relieving chest pain. Their hope was dashed by 1992. Only one out of ten candidates entering clinical trials successfully passes through the gauntlet and reaches consumers,<sup>1</sup> but statistics is little consolation for those who see their projects falling on the heap of nine. Gloomily, the researchers terminated the trial and asked participants to return the unused drug. Many men refused, clutching to the drug as if it was gold. Idiosyncrasies being present in all clinical tests, researchers gave the objection little thought until they heard rumors about the drug’s side effects on sex life and, more important, read a paper on the role of PDE5 in the chemical pathway of erection. Gloom evaporated in the excitement that sildenafil may be a blockbuster after all. This time, their expectation was confirmed by new clinical tests on impotent men. They stumbled on an effective drug for erectile dysfunction Pfizer would market as Viagra.<sup>2</sup>

The accidental origin of Viagra is closer to the rule than the exception in drug discovery. Here serendipity – the knack of finding things not sought for – has won many trophies: sulphur drugs, penicillin, chloroform, vitamins, tranquilizer, and cancer drugs. Often several serendipitous discoveries contribute to the establishment of a major therapy. Take for example insulin for diabetes. Chance observation of flies attracted to the sugar-rich urine of experimental dogs with pancreas removed led to the discovery that the pancreas is causally related to diabetes. Since that discovery in 1889, many scientists tried to extract the pancreas’ secretion and use it as a remedy for diabetes. Some almost made it; others failed, but not necessarily because they were more ignorant. When Frederick Banting, Charles Best, and John Macleod succeeded to extract insulin and demonstrate its therapeutic efficacy in 1921, they designed their crucial experiment on a wrong conception.<sup>3</sup> Microbiologist and historian Alexander Kohn observed: “Nearly all the great discoveries in chemotherapy have been made as a result of a false hypothesis or due to a so-called chance observation.”<sup>4</sup>

Chance, accidents, and serendipity extend beyond drug discovery to scientific discovery at large. Scientific research delves into the unknown. Like all frontiers, the scientific frontier is not a thin line separating light and darkness. It is a broad zone ranging from pockets of puzzles in mostly settled areas to virgin wilderness penetrated only by a few pioneers. The prevalence of chance correspondingly varies.

For matured topics with well-established principles from which specific results can be deduced, accidents happen but are relatively rare. For example, chance had little to do with the discovery of the planet Neptune. Astronomers noticed that the observed orbit of Uranus deviated from theoretical prediction, attributed the persistent deviation to the gravitational effect of an unknown planet, calculated its trajectory and, knowing when and where in the vast sky to look, found Neptune in 1846. Such process of discovery is a glory of science, but should not be made into the stereotype of scientific discovery. The possession of theories such as Newtonian mechanics capable of such precise predictions is not a rule in science, especially in sciences dealing with complex phenomena. Furthermore, powerful deductive theories are not omnipotent. Compared to things such as the living body, the solar system is rather simple. Even so, 159 years separated the discovery of Neptune from Newton's *Principia*, years of hard work engaging the best scientific and mathematical minds. It would take another 84 years for planet Pluto to be observed along its predicted trajectory. A third round, whether a tenth planet exists as theory suggests, still awaits an answer. Is the calculation wrong, are telescopes inadequate, is society unwilling to support the search, or are astronomers unlucky?

Where the frontier of knowledge is wide open, where causes of phenomena mostly hide in the dark, where many scientists deem research most challenging and exhilarating, chance and serendipity play bigger roles. Alexander Becquerel mistakenly developed an unexposed photographic film that sat beneath some uranium salts, saw the salts' image on the film, and discovered radioactivity. Some chance observations led to new sciences or industries. The synthetic dyes industry, one of the forerunners of the modern pharmaceutical industry, traced its origin to the discovery of aniline dye when William Perkin, while washing away some black junk from his failed synthesis of quinine, noticed that the water and washcloth turned purple. Biochemistry, a backbone of biotechnology and biomedicine, was born in 1897, when chemist Eduard Buchner helped in his brother's microbiology laboratory. He added sugar to some juice extract from yeast cells, just as people did to preserve jams and fruits. Instead of being preserved, the juice started to bubble. Surprised, he investigated and found that the chemical process in fermentation, which had been identified with living beings, also occurs outside the living body in cell-free media. This discovery enabled chemists to study biological processes in test tubes and petri dishes, and the field of biochemistry emerged rapidly. Accounts of these and other serendipitous discoveries in science fill books.<sup>5</sup>

Scientific research proceeds with an infinite variety in the availability of data, the maturity of conceptions, and the mix of conviction and uncertainty. Often a major discovery is the culmination of a process with numerous blunders, wrong turns, false hypotheses, missed opportunities, persistent hard work, lucky breaks, rational arguments, insightful conjectures, and accumulating knowledge over decades. Along this tortuous path fogged by ignorance, chance plays on many occasions.

## **How do scientists treat chance?**

From birth into a certain family and culture, fate accompanies us to our graves. Acknowledging luck tacitly renounces merit. It has a psychological leveling effect on social inequalities, as in the familiar remark about the downtrodden: There but for the grace of God go I. Many people contrast chance with logic. Detractors often use chance discoveries to denigrate science as accidental, irrational, arbitrary, and just another myth. They make at least three mistakes. First, they confuse a step in the research process with the whole process consisting of many steps, sidesteps, and backtracks. Second, they confuse the process of research with the result of research. Third, they confuse rationality with absolute certainty. Uncertainty is a human condition, and rational ways exist to reckon with chance, for instance the probability theory.

The scientific community is mainly meritocratic and rational. However, scientists relish at stories of serendipitous discoveries. Even straight-faced textbooks, which usually contain only technical contents and not their paths of discovery, sometimes cannot resist these stories. Scientists are not shy to admit the role of chance in research because they know that fate does not imply fatalism; chance leaves ample room for determination, effort, and sound judgment. Chance happenings in the process of research do not imply that the results of research are irrational, because accidents must pass many further tests before they are justified as scientific results, if they make it at all. Rationality lies in how one handles chance happenings.

A *eureka* moment, when one realizes the solution to a significant problem in a flash of insight, is among the most dramatic of serendipitous discoveries. The eureka idea can be internal or external, depending on whether it happens purely “inside one’s head,” so to speak, or is triggered by some external events. Sometimes an idea pops up in one’s mind, unbidden, under unlikely circumstances. Mathematician Henri Poincaré found a series of Fuchsian functions, for which he had toiled in vain for weeks, during a geological excursion.<sup>6</sup> Molecular biologist Kary Mullis told how he invented polymerase chain reaction, which kicked biotechnology into high gear: “The revelation came to me one Friday night in April, 1983, as I gripped the steering wheel of my car and snaked along a moonlit mountain road into northern California’s redwood country.”<sup>7</sup> In these cases, the idea occurred without external prompting to a mind engaged elsewhere.

The original eureka moment, however, was triggered by the observation of an external event. Legend had it that Archimedes tried hard to find a way to measure the volume of the king’s crown, but to no avail. One day when he slipped into a public bath, he noticed that the water spilled over, upon which he jumped out and ran home, dripping wet and crying: *Eureka* – I have found it. In the chance observation, he realized that he could measure the volume of an irregular object by measuring the volume of the water it displaces.

More often chance encounters trigger not solutions but inspirations, not *aha* but *why*. A glass broken but not shattered or a chicken living after a lethal injection presented not answers but intriguing questions. People bump into puzzles all the time, but most simply ignore them, rushing on in their daily businesses. Credits go to the scientists who stop and ponder about the puzzles they stumble upon, recognize their significances, and make effort to pursue the leads to significant discoveries.

“Chance favors the prepared mind,” remarked Louis Pasteur, a founder of microbiology who had made several serendipitous discoveries himself. Fruitful ideas do not come in an intellectual vacuum. They may pop up at a bus stop or a mountain road, but Poincaré and Mullis had thought long and hard about their problems. Most accidents that led to discoveries occurred in laboratories, which were themselves designed for explorations. Experiments are different from passive experiences, they are active inquiries. An experiment is a question by which scientists try to wrestle answers from nature. The answers may be unexpected, but in setting up experiments, scientists have already primed their minds to pounce on surprises.

We explore the characteristics of a prepared mind in three cases. In the cases of scientists getting their ideas in dreams, we examine the cognitive psychology of thinking and problem solving. The second case we take is one of the most famous serendipitous drug discoveries, that of penicillin. Here we examine how the ability and inability to “connect the dots” facilitated and limited Fleming’s contribution to the development of the antibiotic medicine. Many people would consider our third case, drug screening, to be the antithesis of serendipity. Sure, instead of running into something unintentionally, screening set out with the intention to find something. However, it is also fraught with ignorance and depends on sagacity to pick the gems out from the dirt. In screening, the mind is prepared to take chance systematically.

### **Cognitive psychology of serendipitous discovery**

Stories abound about how a scientist got an idea not while working on the problem at issue but while working on something unrelated, relaxing, or even sleeping. For instance, according to the report of his daughter, physiologist Otto Loewi told his the family about a dream in which he got the idea that would later win him a Nobel Prize: nerve impulses are transmitted by chemicals.

Many historians, especially those of sociological bend, are skeptical if not hostile to such accounts. Inspirations are private experiences, for which the only evidence are the scientists’ own reports. Moreover, they do not fit into the dogma that science is a social construction. Sociological accounts of science often ignore the intellectual dimension of science and treat scientists as mindless things on the same status as scallops and electrons, all being “actants” in the “actant-network model.” Inspirations have no place in such models, which prefer to interpret the scientists’ reports as fictions fabricated for credit grabbing, self aggrandizement, and other power motives.

Some skepticism is healthy. Let us consider one of the most popular dream stories, August Kekulé’s discovery of benzene’s hexagonal ring structure. The benzene ring is a cornerstone of the structural theory of compounds, which is foundational to organic chemistry and instrumental to the dyes and pharmaceutical industries. Probably Kekulé was prone to dozing off and dreaming. He reported that he had illuminating dreams in two separate occasions during the years when he struggled to work out the structural theory. In the second case, he fell asleep while writing a textbook and had a dreamy image of a chain of twisting atoms bending on itself, a snake biting its tail. Awaken, he dropped the textbook and turned enthusiastically to work out the consequences of the hypothesis that the atoms of benzene form a ring.<sup>8</sup>

Was Kelulé's inspirational dream fact or fiction? He talked about it twenty-eight years after its alleged occurrence, during which no account of it can be found. Amassing circumstantial evidence, some historians conclude that he made it up on ulterior motive.<sup>9</sup> Others disagree.<sup>10</sup> In any case, the dream story continues to circulate widely, especially among chemists.<sup>11</sup>

It is impossible to decide whether Kelulé got the benzene-ring idea in a dream, not do I care much about the decision. I am more interested in why the historians' skepticism has not stopped people from retelling the story as if it is true. Perhaps many people find Kelulé's dream story plausible because they too have experienced getting ideas in dreams or dozes, although their ideas may not be price winning. Perhaps the persistent circulation reveals something akin to Aristotle's remark that poetry is more philosophical and serious than history because whereas the historian speaks of particulars, things that have happened, the poet speaks of universals, kinds of thing that *can* happen.<sup>12</sup> Perhaps more important than whether someone did dream is the common psychology of learning and discovery expressed by Kelulé's dream story.

In the state between sleep and awakening, when we have those dreams that we remember, ideas and images occur to us. Most of them are silly, but not necessarily all. It is not impossible that some ideas are answers to questions that worry us. In our daily life, we sometimes encounter something that makes no sense despite our wrecking our brains on it, only to become obvious later and make us wonder in retrospect: How could I be so stupid? Understanding, the transformation from opacity to clarity, involves much effort and is often a prolonged process of knowledge accumulation, but it is often not continuously conscious. "Let me sleep on it" is a common response to a puzzle. We may put it away or have forgotten about it. The answer may emerge gradually or quite abruptly. Sometimes, perhaps prompted by a tiny cue, perhaps as a surprise, the solution pops out. Such phenomena are expressed in common idioms: it strikes me, it dawns on me, it occurs to me. Our newly gained insight may be trivial or an old hat to others. However, our experiences in gaining them make us resonate with scientists' accounts of understanding something new or making unexpected discoveries, perhaps in unexpected circumstances.

The skeptics' strongest argument is that two years before Kelulé's 1856 paper, benzene had already been depicted as a hexagon in a book by French chemist A. Laurent, which Kelulé knew and proposed to translate into German.<sup>13</sup> Did the depiction undermine Kelulé's claim to originality? Apparently not. In line drawings, a circle can mean either a disc or a ring; the ambiguity can only be resolved by context. Laurent used the hexagon in the same page to represent benzene, benzoyl chloride, and ammonia, whose structure was a pyramid. Accompanying explanations suggested that his hexagon depicted not a ring structure but was simply the artist's rendition of a molecule as a chunk capable to bind with other chunks.

A hexagon with "Bz" on it printed in a chemistry book was a suggestive image. Why did it fail to inspire Laurent himself of the benzene ring structure? Why did it fail to inspire Kelulé on the spot? Why did he have to wait for his snake dream? No one can answer this question, but one can venture some guesses. Perhaps his research was not advanced enough. Here I offer a point that is also relevant to serendipitous discoveries. Cognitive psychologists have found that what one sees is at once more and less than what strikes the eyes, being influenced by the meaning one

anticipates or attributes to it. Some experiments on vision find that when reading, we see the meanings and not the shapes of the words. Readers of Laurent's diagram may simply see a chunk and never see the alternative interpretation of a ring. This is not unusual. Serendipitous discoveries often involve a phenomenon that many people have encountered before one person sees it in a new light and recognizes its significance. This happened in the case of antibiotics, as we see later.

Skeptics claimed that Kelulé got the benzene-ring idea from Laurent's diagram and invented the dream story to avoid giving credit to the French, whom the German loathed in that time of rampant nationalism. Such accounts of "the social construction of science" are now popular. They are not impossible, but not more probable than the dream story. Let us assume for argument's sake that Kelulé did get a mental jolt from Laurent's diagram. Does this imply that he stole credit on a sociological motive? Or could he have honestly forgotten the origin of his inspiration? Again cognitive psychology can help. Whatever jolt Kelulé got could not be strong, because he took more than a year to publish the benzene theory. During this time the source of the hexagonal image may have faded from memory. Memory researchers have found that attributing an idea or a piece of information to a wrong source is very common. Many people misremembered how they got the news even for such memorable events as the Kennedy assassination or space shuttle *Challenger* explosion. With no intention whatsoever to lie, eyewitnesses sometimes mistake what they heard afterwards for what they saw on the crime scene. Misattribution is a weakness for memory per se. However, cognitive psychologists argue that it has evolved because it can also be beneficial to a person as a whole. Human memory capacity is limited. Most although not all sources are quite irrelevant to the contents of information, and forgetting them spares scarce mental resources for tasks more important for survival.<sup>14</sup> The cognitive psychology of memory provides an alternative explanation to nationalism-motivated lying: Kelulé did not refer to Laurent because he had a lapse in source memory. They also help us to understand the unending credit disputes in the scientific community. In a culture where people freely exchange ideas and tidbits thereof, many half-baked, it is not surprising that a scientist has an idea and, not remembering where it came from, claims it his own.

The role of the unconscious in scientific creativity is emphasized by cognitive psychologists and reflective scientists. One cognitive psychological model roughly divides a discovery process into four stages. During the familiarization stage, the scientist toils consciously to acquire relevant knowledge and solve the problem. This is followed by an incubation stage, when consciousness turns to something else but the unconscious mind continues to dwell on the problem. Unconscious processes may lead to a eureka moment with an illuminating insight. The eureka moment, however, is not the moment of truth; for more often than not, the *eureka* turns out to be a *blah*. In the final stage, the scientist deliberately scrutinizes the insight and, if it is valid, develops it into a solution of the problem.<sup>15</sup>

Unconscious incubation of ideas sounds vague. However, it has received certain substantiation from cognitive science. In the past several decades, cognitive psychologists and neuroscientists have uncovered vast infrastructures that underlie our conscious mind. Our vision is not like a camera taking in whole pictures. Our memory is not like a stamp on a wax tablet or a file on a computer hard disc, stored and retrieved in one piece. They are far more complex and rightly so;

we *understand* what we see and remember, the camera and computer do not. Simply seeing a balloon or recalling a birthday party involves an incredibly large amount of processing that shape our conscious experience, because it is their end product. We are unaware of these processing, which occur in split seconds and faster. Some of these unconscious processes constitute implicit learning and implicit memory, currently hot topics in cognitive psychology.

Suppose you are reading a paper. Processing starts as soon as light hits your retina, and information does not simply flow one way from the eyes up to the brain. Stored concepts and knowledge are activated by your anticipation and meaning of the previous sentence. Partly under their influence, the current visual input is analyzed into various aspects, processed further, and its gist extracted and partially combined into facets of meaningful objects or concepts. The processing facilitates categorization and understanding at the price of leaving out many details in the input.<sup>16</sup>

The result of visual processing goes through the hippocampus, the brain's memory center. Then its various facets split to be stored in various parts of the brain, leaving a kind of index in the hippocampus to facilitate retrieval. Recollection of an event involves retrieving its bits and pieces and combining them into a memory. Retrieval mechanisms are mainly associative; the word "bank" associatively activates "money" or "river," depending on context. Because association can vary with the cue or strategy of remembering, the activated memory can also vary. Associative processes are also responsible for false recognition, in which people recognize things that they did not encounter or recall imagined events as experienced. A memory can be distorted by repeated retrieval under various conditions, as some associations are strengthened and some weakened. The weakest links eventually drop out, resulting in things forgotten. All these memory processing proceed without our awareness. They are implicit, as cognitive psychologists say.<sup>17</sup>

Analytic processing, gist extraction, and associative activation are information processing mechanisms hardwired into our brains. Without our awareness, they work for the most ordinary of our daily experiences. Their peculiarities are also favorable to scientific and other creativity. False recognition and memory distortion are flaws. However, the associative processes responsible for false recognition can also generate valuable novel links among ideas. The distortion of repetitive memory retrieval can also facilitate selective winnowing of unimportant factors. Connecting ideas and selective forgetting are two processes scientists identify to be crucial to the unconscious incubation that give birth to illuminating insights and serendipitous discoveries.<sup>18</sup>

### **Connecting the dots**

The person who stumbles on an event, recognizes its novelty, and publishes a factual description of it, makes a discovery. However, the rudimentary discovery has little impact if it is not connected to other phenomena, for only in connections are causality explained and significances fully revealed. Making connections, which develops and exploits a discovery, often requires much more knowledge, insight, and effort than the initial description of event. It can lead to a much bigger discovery.

Serendipitous connection of dots led to the discovery that vaccination is a general method for preventing infectious diseases. It occurred during Pasteur's struggle to establish the germ theory of disease, specifically in the case of chicken cholera. To demonstrate that chicken cholera was caused by germs and not some toxins in the blood, it was important to isolate germs from toxins, which was very difficult in those early days. To purify germs, Pasteur extracted them from diseased chickens, grew them in cultures outside the body, and injected the culture into healthy chickens, which would become sick and a new source of germs, hopefully less contaminated with toxins. An autumn day in 1879, he injected a culture into some chickens and found them to be hardly affected. Later, because of a mix up or shortage of supply, the "used" chickens were recycled, together with some new chickens, in experiments to test a fresh virulent culture. This time the new chickens all died but the lucky recycled chickens remained unscathed. A colleague recalled that when Pasteur heard of this surprising development, he "remained silent for a minute, then exclaimed as if he had seen a vision: 'Don't you see that these animals have been vaccinated!'"<sup>19</sup>

Pasteur accidentally obtained the stale culture, according to the traditional account. This account is disputed by historians.<sup>20</sup> However, the dispute changes neither the crux of the discovery nor its serendipitous nature. The major accident in the story was reusing the chickens for a second injection. It led to the serendipitous discovery, which resided less in the source of the stale culture than in the recognition of its effectiveness as a vaccine and the general applicability of vaccination.

Vaccination itself was not new. Chinese and Indians since the eleventh century had been inoculating scabs of smallpox pustules to prevent smallpox infection. The practice passed through Constantinople into Europe around 1700. It was popular there in 1798 when physician Edward Jenner, based on the observation that English cow maids exposed to cowpox were immune to smallpox, introduced "vaccine" (after *vacca*, Latin for cow) derived from cowpox. Smallpox vaccination was accepted strictly based on empirical success, and as such it did not point to the possibility of vaccines for other diseases.

Jenner, perhaps inspired by inoculation, discovered the factual connection between dots: cowpox vaccine and smallpox prevention. Pasteur discovered the theoretical connection between three groups of dot, each represented by a concept. His discovery turned vaccination from a peculiar procedure for a particular disease to a theory connecting germs, vaccines, and disease prevention in general. One no longer needs to wait for a lucky observation to suggest a vaccine for a specific disease. The fruitful idea that a vaccine for a disease can be developed by tinkering on the germs that caused it unleashed a flood of experiments designed to develop vaccines for various infectious diseases.

The first success was Pasteur's vaccine for anthrax, which is discussed in the following chapter. He justifiably asserted: "to look at things solely from the scientific point of view, the discovery of these anthrax vaccines constitutes a considerable advance over the Jennerian vaccine against smallpox, for the latter has never been obtained experimentally."<sup>21</sup> Experiments are not passive observations; they are actively planned according to some conception to look *for* something.



## **The prepared and open mind**

Chance unlocks a door. Most people just walk pass. A few with prepared mind open door and look inside the room. However, without an open mind ready to exploit new possibilities and connect the dots, one may not discover that the room hides more doors that lead to even greater treasures. An interesting case of luck without open mind is the discovery of penicillin, not only as a bacteria-killing mould but also as an antibiotic drug.

The mould story is well known. Alexander Fleming inoculated several dishes with the bacteria staphylococcus, forgot to cover them up, and left for a vacation in the summer of 1928. When he returned, one of the dishes was contaminated by a patch of mould. Observing that the bacteria around the mold were all dead, he had the mould identified as *Penicillium*, extracted its juice, determined its antibacterial effect, and named it penicillin.

Luck graced the incidence in many places. The mould that landed on Fleming's bacteria was not ordinary *Penicillium*; if it were it would not have produced enough penicillin to have visible effects. It was a rare strand extraordinarily productive in antibacterial substance. The substance is effective only when bacterial colonies are quite young. Bacteria grow quickly in summer heat. However, London that summer had a string of nine exceptionally cool days that slowed bacteria growth for the mould's effectiveness. Right mould at the right place at the right time, fortune did smile on Fleming. However, his discovery was not a mere chance; no scientific discovery is. A person with unprepared mind would wash out the penicillin with the dirty dish. In contrast, Fleming tried various ways to concentrate it, classified it as a slow-acting antiseptic, and promoted it as a laboratory reagent to differentiate and select microbes.

Fleming was not the first to come across *Penicillium*. Joseph Lister, the father of antiseptic, noticed the antiseptic effect of *Penicillium* and used it topically to treat a wound in 1884. Fleming went beyond Lister in two important ways. He published a paper on penicillin and gave out samples of his mould to several microbiologists. One of these samples, cultivated as laboratory reagent over a decade in Oxford University, would take part in experiments to realize penicillin's therapeutic value.<sup>22</sup>

Serendipitous discoveries often involve a phenomenon that many people have encountered before one person sees it in a new light and recognizes its significance. The major significance of penicillin is its efficacy as an internal medicine against infectious diseases. This significance neither Lister nor Fleming saw; both stopped at its potential as a topical antiseptic. Penicillin's therapeutic property was discovered by Howard Florey, Ernest Chain, and their Oxford team in 1940, around the time when the British expeditionary force in Dunkirk barely escaped annihilation by German panzers. The property was developed by a huge effort, mostly in the United States, which turned penicillin into an antibiotic drug by the time the Allies invaded Normandy to begin the end of Hitler's reign.

Capitalizing on people's gratitude for the miracle drug that saved countless lives, the popular media constructed a sensational but misinformed image of all glory to Fleming the heroic genius. When the 1945 Nobel Prize for penicillin was awarded, however, it was equally divided among

Chain, Fleming, and Florey. Since then a puzzle persists and incites arguments from many colleagues, biographers, and historians: After he discovered the wonder mould, Fleming could have pressed on to discover the wonder drug, thus saving many lives during the years when the mould sat on the shelf. Why didn't he? It was not that he tried in vain to explore penicillin's therapeutic property; all historical evidence showed that he hardly even tried.<sup>23</sup> What stopped him?

Chain suggested that Fleming did not perform the simple experiment of injecting penicillin into infected mice to test its therapeutic effect not because he was unable to but "because he did not think it was worth while trying."<sup>24</sup> If so, Fleming made not a value but a technical judgment. Antibiotic medicines were very worthwhile to him. He wrote in 1918, moved by the sight of soldiers dying of infection: "I was consumed by the desire to discover . . . something which would kill these microbes, something like salvarsan."<sup>25</sup> He was among the first Britons to test salvarsan, a drug for syphilis and other infections. However, later when penicillin into his lap, all he proffered were data on its instability and nontoxicity and a few trials to apply it topically on shallow wounds.<sup>26</sup> How did his consuming desire for antibiotic drugs reconcile with his indifference to the golden opportunity of developing one – if he realized it was an the opportunity?

One reason for failing to connect the dots of penicillin and antibiotic therapy, attested by Fleming himself, was that he was a microbiologist and lacked the chemical expertise to perform the requisite experiments. Relevant knowledge is essential for scientific investigation, not the least for therapeutic properties, which are subtle and difficult to ascertain. Here Chain, a biochemist, and Florey, a pathologist with chemical training, had definite advantages. Their expertise enabled them to probe penicillin in a deeper level to reveal its therapeutic potentials. "Penicillin" for Fleming referred to the crude extract, which was just the filtered broth in which the mould was grown. After Florey and Chain, "penicillin" refers to the purified chemical compound that is the active principle of Fleming's mould juice. The latter meaning facilitated precise measurement, experimentation, scientific understanding, and practical manipulation. In this regard, Fleming was disadvantaged in expertise.

Nevertheless, Fleming's the disadvantage was not debilitating. As Chain pointed out, many animal experiments required little chemical expertise and were completely within Fleming's repertoire. Furthermore, it is not unusual for a scientist to lack competence for solving a particular problem, for scientists are mostly specialists and interesting problems often involve factors in widely disparate domains. Under such situations, common practices are to seek collaborators or hire assistants to complement one's own resource. Fleming did it too. He consulted a fungi expert to identify the godsend mould as *Penicillium*. His two young assistants were not ignorant of biochemistry. They made significant progress in concentrating the mould juice and performing biochemical experiments. Despite their eagerness, Fleming gave them little support, assigned them elsewhere after a few months, and threw their results into a drawer, unpublished.<sup>27</sup>

Proponents of the lonely-hero image blamed people for ignoring Fleming's claim on penicillin antiseptic, as if he had worked to generate interest. Attention is a scarce commodity that one must fight to attract, and one must fight harder to win support and collaboration. Interesting

problems abound and everyone is busy. It is incumbent on scientists to make effort in bringing out the importance of their own discoveries to drum up enthusiasm. Where Fleming tried, he succeeded. His paper “On the antibacterial action of cultures of a *Penicillium* with special reference to their use in the isolation of *B. Influenz*” emphasized the use of penicillin as a laboratory reagent. For this use he had interested several microbiologists. It was very different with medicinal potentials. Only at the very end did the paper state briefly: “It is suggested that it [penicillin] may be an efficient antiseptic for application to, or injection into, areas infected with penicillin-sensitive microbes.” In the many papers he wrote during following twelve years, only one mentioned penicillin’s medical future, that it would be likely to be “used in the treatment of septic wounds.” These were Fleming’s strongest medical claim for penicillin. They suggested only topical treatment of wounds. Even as antiseptic, his claim remained speculative; he gave up finding empirical supports after a few unsuccessful trials.<sup>28</sup> When the author considers his own claim not worth the effort to substantiate, the reader can hardly be blamed for shrugging.

Some sociologists suggest that people were indifferent because Fleming was a poor speaker. Social skills are important for anyone, scientists including, but scientific persuasion should not be confused with snake-oil salesmanship. In rational arguments, solid data and sound reasons are more eloquent than flowery rhetoric. Anyone can say, this stuff here will make a good drug, but the conjecture is empty without evidence that the stuff can satisfy stringent conditions of efficacy and safety. Evidence for the stuff’s therapeutic properties is laborious to gather. Florey and Chain made the effort that Fleming spared. Their paper “Penicillin as a chemotherapeutic agent” generated more enthusiasm than Fleming’s paper not because their prose was better; Fleming wrote well and clearly. Their claim of antibiotic therapy was more significant than Fleming’s suggestion of antiseptic. More important, they backed up their claim with substantial data on a series of controlled animal experiments. Lack of evidence, not lack of words, was what harmed Fleming’s case most.<sup>29</sup>

Fleming was enthusiastic about Florey and Chain’s paper. A week after its publication, he showed up in Oxford to the surprise of Chain, who thought him dead; so quiet was he on penicillin for so long.<sup>30</sup> An explanation for the quiescence was suggested by Henry Dale’s obituary for Fleming. The Inoculation Department at St. Mary’s Hospital in London, where Fleming worked, was not conducive to penicillin research.<sup>31</sup> The adversity is more cultural than administrative. Fleming, as professor and assistant director of the department, had considerable freedom to choose his research, which he exercised in studying salvarsan and sulfanilamide.<sup>32</sup> However, probably his choices were biased by his department’s communal belief that vaccination was the only way to fight infectious diseases and internal medicine was hopeless.

The paralyzing pessimism on antibiotic medicine was local to Fleming’s community. Drug therapy was difficult and had suffered many setbacks, but its failure was far from total. Salvarsan, the syphilis drug Fleming once earned to emulate, was ineffective for some cases and difficult to administer, but at least it offered some hope for some patients. The scientific community at large had not despaired of improvements. Several months before Fleming discovered penicillin, Gerhard Domagk at Bayer quietly started a painstaking screening program that would result in the discovery of the first effective antibacterial drug, sulfanilamide.<sup>33</sup> Both scientists had access to the literature, but they made diametrically opposite technical judgments about the feasibility of antibacterial medicine. Scientific research is always risky and fraught

with setbacks, therapeutic research especially so. Domagk judged the risk worthwhile and his optimistic commitment sustained him through countless failures for almost four years. He might not have won the Nobel Prize had Fleming proceeded to develop penicillin that, being superior to sulfanilamide, would have preempted his result. Fortunately for him although not for victims of infection, Fleming gave up at the tiniest negative result, imbued with the pessimism of his local communal belief. Citing Fleming's predicament, Chain said it was "a good example of how preconceived ideas in science can stifle imagination and impede progress."<sup>34</sup>

Preconceived ideas are not themselves bad; in fact, they are necessary for any inquiry. Without some hunch that it might be significant, Fleming would have simply washed the *Penicillium* with the dirty dish. Albert Einstein asked: "If the researcher went about his work without any preconceived opinion, how should he be able at all to select out those facts from the immense abundance of the most complex experience, and just those which are simple enough to permit lawful connections to become evident?"<sup>35</sup> To investigate the unknown, one must make some initial conjectures; otherwise, one cannot even decide what direction to look. However, scientists must be ready to criticize and modify their preconceived ideas. Examples abound of research born on wrong conjectures leading to important results.<sup>36</sup> Here the disparate responses of Fleming and the Oxford team to similar evidence are illuminating. Neither party was initially interested in therapy. Difficulties for internal medicine were well known. The worst was toxicity: substances powerful enough to kill germs in the body were thought likely to be too toxic for the patient. Fleming and the Oxford team both injected some penicillin into mice and found it nontoxic. These initial nontoxicity results were not definitive, because the dosages were not certain, and in medicine, dosage makes the poison. Nevertheless, they were first shots directed at the Achilles heel of any preconceived idea about the impossibility of drug therapy. Chain considered their nontoxicity result the most important data that turned the team toward penicillin as chemotherapy and motivated subsequent experiments. Fleming reported his result and did nothing more.<sup>37</sup> Science is impeded not by preconceived ideas but by the failure to challenge them in light of evidence.

A blank mind is an impotent mind, not a prepared mind. A prepared mind has preconceived ideas but is simultaneously eager to seek alternatives and ready to change. Among the most precious preconceived ideas are that *I can be wrong* and that *my community is not the whole universe*. Dale, Nobel laureate for discovering neurotransmitters, had also reflected on the nature of scientific research. He wrote that chance favors "him who, while continuously busy with the work of research, does not close his attention from matters outside his principal aims and immediate objective but keeps it alert to what unexpected observation they may have to offer."<sup>38</sup>

### **Taking chance systematically**

Several conditions make chance prominent in drug discovery. Animal bodies, medicines, and their interactions are so complex as to defy complete understanding despite tremendous scientific advancement. For a long time they stayed in almost total darkness. Ignorance, however, did not quell people's craving for something to relieve sickness and suffering. In desperation they leveraged what little knowledge they possessed to the fullest and took risk to try new things. Memories of the errors they made and the prices they paid linger in the word "pharmacy," the

Greek *pharmakos* meant both remedy and poison. Fortunately not all accidents were fatal; some led to valuable solutions. By trial and empiricism, our ancestors in various cultures accumulated knowledge on diagnostics, prognostics, and medicines. Many folk remedies are placebos, many are effective, and many are still in use. Their increasing popularity in western countries as alternative medicine irritates some mainstream physicians.<sup>39</sup>

A drug is a chemical that is effective and safe in treating a disease or its symptoms, hence drug therapy is also known as chemotherapy, as distinct from surgery, radiotherapy, or physical therapy. The first drugs were chemicals isolated from herbs of known effectiveness, for instance the painkiller morphine from opium and the malarial drug quinine from cinchona bark. The apothecaries that produced them capitalized on the fruits of eons of chance discoveries to become a cornerstone of the pharmaceutical industry. Besides nature, drugs have a second source in chemical laboratories that combine atoms and molecules to synthesize novel compounds. Manufacturers of fine chemicals, especially dyes, became another cornerstone of the pharmaceutical industry.<sup>40</sup>

Nature offers millions of herbs and organisms, chemists can synthesize as many compounds. How to find in this haystack of substances the few with therapeutic potentials? Four Gs – *Geduld, Geschick, Glück, and Geld* (patience, skill, luck, and money) – were the answers offered by Paul Ehrlich, commonly acknowledged to be the father of chemotherapy. Based on the observation that different dyes stuck specifically to different kinds of cell, he developed around the turn of the twentieth century a “receptor theory” of specific chemicals binding to specific receptor sites on cells. A drug molecule, especially a toxin, could bind to a bacterium and kill it. The receptor theory, which would become a foundation of pharmacology half a century later, was speculative in his time.<sup>41</sup> Nevertheless, it encouraged him to synthesize hundreds of arsenic compounds and test them against bacteria that cause syphilis, a major scourge of his time. Working together with Sahachiro Hata, they discovered in 1909 the drug salvarsan.<sup>42</sup>

The systematic way in which Ehrlich screened and explored the biological activities of a class of chemicals to target a specific disease set the paradigm of drug discovery in industry. A similar screening program would lead Domagk to discover the precursor of sulfanilamide in 1932. Dumb and dull at first blush, screening appears to be the opposite of serendipity. Yet of the three elements of serendipity – chance, sagacity, and inadvertency – it lacks only the third. Luck is crucial; both salvarsan and sulfanilamide were near misses.<sup>43</sup> The screening approach is a deliberate attempt to make chance discoveries. Acknowledging that the inability to predict compound actions makes one dependent on chance to find effective drugs, scientists increase their chance of success by effort. Screening efforts are laborious but not blind; scientists employ whatever knowledge they have to design effective search strategies. It is like trawling for fish, the chance of a catch increases if one has the sagacity to refine the net and find a good place to cast it.

Nature is a vast repository. Soil microbiologist Selman Waksman started in 1939 to screen soil microbes for activities against pathogenic bacteria. Over the years his group isolated and tested some 10,000 cultures, from which came 10 drugs. The most important was streptomycin for tuberculosis, for which he won the Nobel Prize.<sup>44</sup> This was only the beginning of massive screening programs. Sponsored by pharmaceutical firms, government agencies, and universities,

bioprospectors combed every corner of Earth to collect samples from the land, air, and sea, sometimes guided by the wisdom of folk medicines. From nature's cornucopia came the leads to most antibiotics, immunosuppressants, anticancer substances, and over a hundred of the most important drugs. Then in the 1970s, the number of new substances plummeted. After screening literally millions of soil microorganisms, new tests kept turning up the same old stuff. Nature is bountiful but exhaustible.<sup>45</sup>

The pendulum swung back to the other source of drugs, synthetic chemicals. Medicinal chemists had synthesized many drug-like compounds over the decades. Their productivity was boosted since the late 1980s by combinatorial chemistry, which can generate new compounds a thousand times faster at lower costs. Libraries of millions of chemical compounds are amassed in industrial and academic laboratories. Computers, robotics, miniaturization, and other technologies of automation enable researchers to process them efficiently. High throughput screening can handle 100,000 compounds a day.<sup>46</sup>

Massive screening is not necessarily blind screening. Arbitrary searches through the greatest libraries had been tried with dismal results. Much more productive is focused screening, which is guided by scientific knowledge to concentrate on smaller libraries with relevant themes. Chance needs the help of knowledge in drug discovery.

Drug therapy involves the interaction between therapeutic chemicals and living bodies. So far, we have looked only at the chemical side. Equally important is the biological side, the body and its functions and malfunctions. Knowledge from the life sciences, especially microbiology, biochemistry, and molecular biology, become increasingly important in pharmacology.

Ehrlich likened a potent drug to a magic bullet. A bullet can work its magic only if aimed at the proper target. The targets for infectious diseases are apparent after the establishment of the germ theory in late nineteenth century. They are alien bacteria tracked down by microbe hunters and cultured in laboratory dishes so convenient for target practice. But where do the magic bullets aim in diseases such as cancer or ulcer? The question cannot be answered without some knowledge of disease mechanisms. Without such knowledge, drug discovery relies on mere empiricism, finding things that work without knowing why they work.

The body is a huge chemical factory with myriad biochemical pathways – chains of biochemical reactions – that maintain the normal physiology of life. Sometimes, an errant link in the chain causes a pathway to malfunction, resulting in a disease. Then a cure may lie in repairing the link and recovering the pathway's normal function. Errant links in biochemical pathways present targets for drugs. To identify them require detail knowledge about the pathways, which come from biochemistry.

Since Buchner demonstrated fermentation outside of the living body in 1896, biochemistry progressed fast. By the 1970s it was matured enough to step into the center stage of pharmacology. Biochemists identify many macromolecules that control strategic links in the body's biochemical pathways. Pharmacologists choose as drug targets those macromolecules whose mechanisms are susceptible to intervention by small chemical molecules. Drug therapy currently works on about 500 targets.

About a quarter of known drug target are enzymes that facilitate crucial chemical reactions. An example is the COX2 enzyme, which aspirin blocks to relieve pain and inflammation, as we saw in the preceding chapter. About one-half of drug targets are receptors on cells, as Ehrlich predicted half a century ago. Receptors are macromolecules that sit on the surface of a cell and are crucial to the normal functions of healthy bodies. A specific kind of receptor receives specific chemical messengers from other parts of the body that regulate a specific process in the cell. If that process goes wrong in sickness, a drug can hopefully set it right by binding to its regulating receptors. Genes can also be drug targets, although their numbers are rather small at present. The impact of genetics in pharmacology is increasing dramatically since the 1990s. Genomics, which has sequenced the human genome, and proteomics, which aims to catalog and unravel all human proteins, hold out promises for 5,000 or more potential drug targets. Practical therapeutic exploitation of these targets, however, requires much more research into their physiological roles and interactions with drug-like chemicals.<sup>47</sup>

Disease mechanisms, targeted remedial actions, and other scientific concepts turn drug discovery from mere empiricism to rational empiricism. Previously, people tried anything without any prior idea whether it would work. Trial and error still plays a major role, but now it is guided by partial knowledge of drug targets. Knowledge of a target's structure gives pharmacologists some idea of what the new drug should be like. Drug discovery takes on a sense of rational design.

It costs around \$800 million and 10 to 15 years to develop a new drug and bring it to market.<sup>48</sup> With so much money and patience are at stake, people make utmost effort to complement luck. Suppose after considering medical, financial, social, and technical factors, the decision is made to find a drug for a specific disease. A typical process begins with identifying the potential targets and confirming that the chosen targets are indeed critical to the disease mechanisms. Target selection and validation draw on knowledge in pharmacology, biochemistry, and increasingly molecular biology.

A drug target is a macromolecule and is often compared to a lock. Given a target, the next step is to find a key for it and for it alone; a key that fits also into other locks would generate unwanted side effects. Researchers usually, although not necessarily, begin with screening the appropriate chemical libraries to search for leads – chemicals that roughly fit the target. Leads are like appropriate blanks for a lock. To cut the blanks into a key, researchers must optimize the lead chemicals. They synthesize hundreds of chemicals that vary on a lead's basic structure and test them in animal models. Besides therapeutic effectiveness and toxicity, they also look for variants that are better absorbed, metabolized, distributed, and excreted. After many iterations of tinkering and testing, they find a candidate ready to be tried in human beings. This preclinical phase of drug development consumes on the average about five years and a third of the costs. The clinical trials, which come in three phase, each engaging ten times more subjects than the preceding one, take another five or six years and about half of the costs. They knock out ninety percent of the candidates; what work in mice do not necessarily work in humans. Finally, the triumphant few obtain approval from government regulators to go to physicians and patients.<sup>49</sup>

Drug design guided by knowledge of targets has produced an abundance of diverse drugs. Familiar ones are ulcer drugs (Tagamet) and statins that reduce cholesterol (Lipitor and Zocor).

Less familiar ones are the leukemia drug Gleevec and several drugs for HIV/AIDS. Development of HIV drugs reveals how much drug targets have been refined since Fleming's days.

Microbe hunters pinned down the Human Immunodeficiency Virus as the culprit of Acquired Immunodeficiency Syndrome in 1983. Antibiotics kill germs but not viruses. A virus, being less than a cell, cannot reproduce on its own. To reproduce, it must sneak into a cell, merge into its DNA, and commandeer its facilities. This viral reproductive process is susceptible to attack at several points. Investigation of HIV's life cycle identified three targets. They led to three types of drug, now making up the expensive therapeutic cocktails that, although short of a cure, enable many AIDS patients in the developed world to lead a normal life for a long time.

The first drug target is an enzyme that enables the HIV virus to incorporate its genetic material into the human DNA. Inhibiting this enzyme is the job of AZT and other drugs. The second target is an enzyme that produces the protein essential for the HIV to replicate. Drugs such as Viracept are designed to suppress this enzyme. The third and newest class of drugs targets a receptor through which the HIV makes its way into a human cell, thereby denying entry to the virus. These drugs were developed by methods ranging from empiricism to computer-aided design. AZT resulted from an extensive screening of natural products, which found a lead in a substance derived from salmon sperm. Viracept is an outstanding case for designing a drug almost from scratch using computer modeling, based on knowledge of the structure of the target enzyme and the mechanisms of interaction between the target and potential drug chemicals.<sup>50</sup>

Designing from scratch remains an ideal that boasts only a few successes besides HIV drugs. Most drug development projects employ a rational mix of empiricism and theory: focused screening yields leads, which are optimized by computer modeling. It is estimated that for each marketable drug, hundreds of thousands of compounds are screened or synthesized. The rejects are not total wastes, however. Some of them have been extensively scrutinized before they are discarded, and knowledge about them remains and can be exploited for other drugs. This is a source of serendipity in drug discovery. A substance intended for one disease sometimes turns out to be efficacious for another instead. The chemical active in AZT was originally developed for cancer therapy, and that in Viagra was for heart ailment. Screening for antibiotics turned up substances with surprising uses, for instance in drugs that suppress the body's immune system and prevent it from attacking alien organs, thus revolutionizing organ transplantation. The unexpected values of failed chemicals would be missed by the one-track minded. To recognize them, as in all chance discoveries, researchers must be open to areas sometimes quite distant from their core expertise.

Productivity for drug discovery declines recently. Increases in research funding are not matched by increases in the number of new drugs. Perhaps this is a manifestation of what economists call the law of diminishing return. Perhaps most "soft targets" have already fallen, leaving chronic diseases such as cancer, which are much more difficult to treat. Molecular biology, biotechnology, and genomics create waves of optimism, but spectacular scientific successes have so far led only to modest therapeutic successes. Of course researchers should be prepared to criticize and modify their approaches. To blame science for "the fall of modern medicine," however, is unfair. Perhaps the case of biotechnology is similar to that of information



technology. Computers proliferated in the 1970s. Although they were supposed to make people work more efficiently, productivity of the national economy was anemic for two decades. As late as the early 1990s, a Nobel laureate economist quipped that one saw information technology everywhere, except in productivity. Then productivity perked up in the late 1990s, grew with a vengeance and did not subside during the subsequent recession. Economists attribute most of the growth to information technology, which finally bears fruit after climbing a steep learning curve. Chance favors a prepared mind. Success favors an open and persevering mind.

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## Notes

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11. Roberts. *Serendipity*, pp. 80-82. Kohn, *False Prophets*, p. 216.
12. Aristotle, *Poetics*, 51b.
13. Wotiz and Rudofsky, Kelulé's dream. Kohn, *False Prophets*, p. 216.
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27. Macfarlane, *Fleming*, p. 251. T. I. Williams. *Howard Florey*. New York: Oxford University Press (1984), p. 96-97.
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29. Williams. *Florey*. ch. 3.
30. Macfarlane. *Fleming*, p. 178.
31. Kohn, *Fortune*, p. 77-78.
32. Macfarlane. *Fleming*. p. 250.
33. Kohn, *Fortune*, pp. 47-48. Roberts, *Serendipity*, pp164-9.
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35. Quoted in G. Holton. *The Scientific Imagination: Case Studies*. New York: Cambridge University Press (1978), p. 99.
36. One example was the discovery of cancer drug cisplatin. Its origin had nothing to do with cancer or drug. Biophysicist Barnett Rosenberg conceived the idea that electric currents may affect cell growth. He designed an experiment that passed an electric current through a soup of chemical nutrients in which bacteria grew. For electrodes he decided to use platinum, thinking that the inert metal would minimize spurious chemical effects. After two hours of electric current, the bacteria in the soup stopped dividing, instead, some continued to grow to enormous sizes. To pinpoint the cause of this phenomenon, he did numerous experiments, going into blind alleys and new directions. It turned out that his original ideas about electric current and platinum were both wrong. The current had no effect on bacteria growth and division. The platinum electrodes, under the experimental conditions, produced a trace amount of a rare compound *cis*-diammonia platinum chloride. It was this compound that prevented the bacteria from dividing. In his paper on this result, Rosenberg suggested that similar metal ions might also inhibit division of other bacteria or cells. If so, they could be useful in cancer therapy by stopping cancerous cell division. This time his conjecture turned out to be right. Research along this line led to cisplatin (marketed as Neoplatin), a treatment for a certain type of testicular cancer in men and ovarian cancer in women. J. Mann. *The Elusive Magic Bullet: The Search for the Perfect Drug*. New York: Oxford University Press (1999), pp. 149-151.

37. Williams, *Florey*, pp.105-106.
38. H. Dale. Accident and opportunities in medical research. *British Medical Journal*, 2: 455 (1948). Quoted in Kohn, *Fortune*, p. 2.
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41. A. Maehle, C. Prüll, and R. F. Halliwell. The emergence of the drug receptor theory. *Nature Review: Drug Discovery*, 1: 637-641 (2002).
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43. The near misses of Ehrlich and Domagk both involved the test methods that they used. Ehrlich synthesized the compounds and tested them in cultured cells outside the body, and found nothing useful for treating syphilis. Later Hata retested the compounds in rabbits infected with the bacteria, and found that compound number 606 was changed in the body into something that kills the bacteria. Form compound 606 came salvarsan. (Porter, *Greatest Benefit*, pp. 451-452.)  
 Domagk's case was just the opposite. He received dyes synthesized by his colleagues and tested them in mice infected with various pathogens. A red dye, prontosil, was effective against streptococcus. He gave it to his four-year old daughter who developed a severe streptococcus infection from a pin prick and saved her hand from amputation. After the results on prontosil was published, J. and J. Trefouel found it to be ineffective against streptococcus in culture. Prontosil was broken down into two parts in the body, and only one part, sulfanilamide, was the active principle. Sulfanilamide was synthesized by Paul Gelmo in 1908 and was used as an intermediary in dye manufacture. Its therapeutic properties were not recognized until 1935. Since then many analogs of sulfanilamide were synthesized and tested, resulting in a large class of sulfur drugs. (Roberts, *Serendipity*, pp. 164-169).
44. Kohn, *Fortune*, pp. 130-5. Mann, *Magic Bullet*, pp. 63-5.
45. R. Seethala and P. B. Fernandes. *Handbook of Drug Screening*. New York: Basel (2001), pp. 1-4.
46. L. J. Gershell and J. H. Atkins. A brief history of novel drug discovery technologies. *Nature Review: Drug Discovery*, 2: 321-328 (2003).
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48. The \$ 800 million is the average cost, in 2000 dollars, of a new chemical entity developed in 1983 –1994. It covered the out-of-pocket costs that pharmaceutical firms paid from creating the entity to obtaining FDA approval to market it. The result was obtained by the independent academic Tufts Center for the Study of Drug Development. (J. A. DiMasi, R. W. Hansen, and H. G. Gabowski. The price of innovation: new estimates of drug development cost. *Journal of Health Economics*, 22: 151-185, 2003. It is also available at [www.csdd.tufts.edu](http://www.csdd.tufts.edu)).

Because of concern for drug prices, the costs of drug development are subject to much debate. Numbers ranging from \$ 110 million (Public Citizen) to \$ 880 million (Boston Consulting Group) are being cited. The Tufts research is the best designed, most extensive, and hardest scrutinized. Its earlier result, using a similar methodology, for drug development in 1970 –1982, was reanalyzed by the U.S. government's Office of Technology Assessment (OTA) and the consumer group Public Citizen (PC). These studies

were reviewed by M. Dickson and J. P. Gagnon. Key factors in the rising cost of new drug discovery and development. *Nature Review: Drug Discovery*, 3: 417-429 (2004). Here is a summary:

<u>Study (period covered)</u>	<u>Average cost (2000 dollar)</u>
Tufts (1970 – 1982)	\$ 319 million pre-tax
reanalyzed by OTA	\$ 445 million pre-tax
reanalyzed by PC	\$ 293 million post-tax
Tufts (1983 – 1994)	\$ 110 million post-tax
	\$ 802 million pre-tax

After critical review, the OTA mainly agreed to Tufts' analytic methodology. It also compared Tufts' data with other sources and took account of "tax breaks" that pharmaceutical firms got for their R&D expenditure. PC's low number was obtained mainly by ignoring the cost of capital and thus going against the standard practice in economic analysis. Drug development also benefits from research funded by taxpayers. Because the costs of public-funded research are not included in the figures quoted, the actual costs of drug R&D are even higher.

The two studies by Tufts show that drug development costs have risen dramatically over the decades. Most of the additional expenditure occurs in clinical trials, which are becoming longer and involving more subjects. This may be due to increasing regulations, concerns about safety, and the nature of the diseases to be treated. With drugs already available for many acute diseases such as infection, new drugs increasing aim at chronic diseases such as cancer. Because these drugs have to be taken for a long period of time, testing for their safety is more difficult and hence more expensive.

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