Clinical investigators as critical determinants in pharmaceutical innovation

Clinical investigators perform a critical role in the process of drug development that is often overlooked by industry.

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Pharmaceutical innovation

Pharmaceutical innovation is a complex, interdisciplinary process that remains central to success of the pharmaceutical industry and the practice of medicine. The development of new drugs is time-consuming, expensive and risky, and the costs and time required for drug development continue to increase[1-6]. A number of investigators have estimated that 12 years or more and approximately $231 million (in 1987 dollars) are required to develop a new drug, from synthesis to approval by the Food and Drug Administration (FDA)[1-6]. Despite these barriers, pharmaceutical companies have successfully developed a broad range of innovative and therapeutically important drugs. Although most of the strategies for reducing drug development time have focused on streamlining regulatory policies, we believe that the regulatory process itself is not the only key determinant of the speed of development of a new chemical entity (NCE).

Information drives pharmaceutical companies and other research-based organizations[7-9]. Consequently, successful pharmaceutical innovation depends on the effective management of numerous sources of information and those who produce it[8]. Many authors have advocated rational drug design (setting development priorities for chemical entities based on structure–activity relationships) as a means of reducing development time[8]. However, it is not well understood how to channel the pipeline of pharmacological data into clinically useful drugs, or whether understanding of structure–activity relationships is the most significant influence on development time. The factors that affect the transfer from basic scientific information to clinical applications may be the most important determinants of the time required to develop drugs. We present one key factor (the interest of the clinical investigator), which has been underplayed in past analyses of the speed of drug development.

Drug development from lead observation to FDA approval

To examine how information production and use influence the time required for drug development, we analyzed the significant events[10] in the development of five structurally related purine analogue drugs discovered at Burroughs Wellcome and Syntex. We focused on three important determinants of the time required for FDA approval of these drugs: the availability of relevant scientific information, the information management infrastructure of the pharmaceutical organization, and the roles of researchers who provide and use information. We also considered the effects that simultaneous laboratory activities, the external environment and the regulatory influences of the FDA had on the rate of drug development. The purine analogue drugs were chosen for this study because drugs for diverse indications emerged from the findings of two scientists conducting basic research, George Hitchings and Gertrude Elion, and the time required to develop these drugs varied widely. This situation presented the opportunity for the authors to identify for each drug developed the scientific finding that established the potential for drug development. We defined this finding to be the lead observation (see Methods). By examining the events that led to the approval of each drug, the authors determined the factors that promoted rapid drug development in some instances and led to protracted development in others.

The lead observation

In 1950, George Hitchings succinctly stated the research goals of his laboratory group at Burroughs Wellcome[11].

> A study was begun in these laboratories in 1942, of the relationships between chemical structure and the ability of certain pyrimidine derivatives to serve as precursors for or to modify nucleic acid synthesis. . . . It was felt that such studies might lead to fundamental knowledge of the role of pyrimidine and purine bases in growth and of the part played by folic acid in the synthesis of these bases. It was felt that new chemotherapeutic agents might be discovered by this means since, it was argued, parasitic tissues in general depend for survival on a more rapid growth, hence a more rapid synthesis of nucleic acid, than host tissues. This argument applies equally well to bacterial, viral, rickettsial, and neoplastic diseases.

This statement demonstrates that Hitchings envisioned the potential for applying purine analogue pharmacology to several indications at approximately the same time. Hitchings specifically included two of the eventual clinical applications for purine analogues, antineoplastic and antiviral drugs, in his initial disclosure. His hypothesis also shows Hitchings' understanding that agents might also be discovered that modified other cell types that proliferate more rapidly than most host tissues, such as stimulated lymphocytes, bacteria, virus and parasites. He mentioned nothing about the management of gout, although the mechanism by which the disease occurred was known by this time, and by 1944, Hitchings had investigated inhibitors of xanthine oxidase, the enzyme involved in hyperuricemia and gout[12]. Hitchings' statement meets each of the criteria for a lead observation. More importantly, his statement does not merely constitute enabling of one but, at minimum, four drugs used for a number of apparently unrelated clinical indications. In fact, as lymphocytes were known to turn over reasonably rapidly and also to mediate immunity, he could have targeted immunomodulation as yet another potential indication. Table 1 highlights some of the significant events in the development of each purine analogue drug studied.

Variations in drug development time

Despite the almost simultaneous availability of a panoply of chemical agents that could be tested as drugs, and despite basic understanding of the pathophysiology of each of the targeted disease processes, the time required to develop purine analogue drugs for different medical indications varied widely. The date of the lead observation and approval for each drug are shown in Fig. 1.

Table 1 Significant events in the development of five purine analogue drugs

6-Mercaptopurine	
1947	George Hitchings of Burroughs Wellcome (BW) collaborated with the Sloan-Kettering Institute (SKI) to test whether purine analogues had antineoplastic activities[12].
1949	SKI tested 2,6-diaminopurine in mice[19].
1951	Joseph Burchenal (SKI) used 2,6-diaminopurine to produce remission of chronic granulocytic leukemia (CGL) in adults, but patients experienced severe nausea and vomiting[20].
1951	Gertrude Elion's laboratory (BW) synthesized and screened more than 100 purines and found that substitution of oxygen by sulfur at the 6-positions of guanine and hypoxanthine produced purine utilization inhibitors[67].
1951	6-Mercaptopurine (6-MP) and 6-thioguanine (TG) were tested at the SKI for antitumor activity[68].
1953	Burchenal and colleagues found that 6-MP produced remission of acute leukemia in children[69], and the FDA approved 6-MP for clinical use.
Azathioprine	
1958	Robert Schwartz and William Dameshek studied the action of 6-MP on the immune response, hypothesizing that immunoblastic lymphocytes resembled leukemic lymphocytes.
1958	Schwartz and colleagues showed that rabbits given 6-MP did not mount an immune response against a foreign antigen[24].
1959	Schwartz and Dameshek demonstrated that animals could be made tolerant to a particular antigen and remain immunoreactive to others[25].
1960	Roy Calne, prompted by Schwartz's research, examined the effect of 6-MP on kidney transplant rejection in dogs[26,27].
1961	Calne asked the Elion laboratory for new chemical entities (NCEs) to investigate and found azathioprine superior to 6-MP at preventing rejection of canine homografts[23].
1961	At Schwartz's suggestion the Elion lab studied the dose response and synergism of purine analogues in antibody response of mice to sheep red cells[22].
1963	J.E. Murray and colleagues found immunosuppression with azathioprine and prednisone to allow successful transplantation of kidneys from unrelated donors in humans[70].
1968	The FDA approved azathioprine for clinical use.
Allopurinol	
1944	Doris Lorz and George Hitchings of BW began to examine purines as substrates or inhibitors of xanthine oxidase (ref. 12 and Abstr., Am. Soc. Biol. Chem., 1950).
1948	Purine analogues were found to inhibit *Lactobacillus casei* acid formation[11,67,71–73].
1950	Lorz identified many substrates and inhibitors of xanthine oxidase (Abstr., Am. Soc. Biol. Chem., 1950, and Abstr., Am. Chem. Soc., 1956).
1954	Numerous studies of urinary metabolites suggested that extensive metabolic transformation of 6-MP occurred *in vivo*[13,14,74].
1962	Elion's group selected allopurinol, a potent inhibitor of xanthine oxidase that was nontoxic for *in vivo* studies[13,14,74].
1963	R. Wayne Rundles and G.B. Elion's group found allopurinol to inhibit oxidation of 6-MP in patients with chronic granulocytic leukemia (CGL) in a dose-related manner, and discovered that the antileukemic activity of 6-MP increased proportionally[30,31].
1963	Rundles remarked that allopurinol decreased serum and urinary concentrations of uric acid, which presented a possible treatment for gout and other forms of hyperuricemia[30,31].
1964	T.F. Yü and A.B. Gutman discussed that allopurinol could prevent uric acid crystal formation in the joints and kidneys[75].
Acyclovir	
1947	Hitchings arranged collaborations with outside laboratories to test purine analogues for antiviral activities[12].
1949	R.C. Thompson and colleagues showed 2,6-diaminopurine had antiviral activity against vaccinia virus, but its toxicity in animals led the group to abandon antiviral development[40,41].
1968	F.M.J. Schabel showed that arabinosyladenine (Ara-A) inhibited the growth of DNA and RNA viruses[42]. This finding renewed Elion's interest in antivirals.
1968	J.L. Rideout (BW) synthesized Ara-DAP (ref. 33, 76).
1968	D.J. Bauer reported that Ara-DAP was highly active against herpes simplex virus and vaccinia virus, and less cytotoxic to mammalian cells than Ara-A42.
1970	Elion's group moved to North Carolina, and Howard Schaeffer joined BW as head of the Organic Chemistry Department (ref. 33, 76 and G.B. Elion, personal communication).
1971	Elion's lab studied purine arabinosides' structure–activity relationships (including the acyclic purines that Schaeffer brought to BW), sought better synthetic methods, and ran metabolic studies in mice[33].
1978	Bauer found that acyclovir (ACV) was 100 times as active as Ara-DAP, and not cytotoxic to mammalian cells at concentrations 1000× those required for antiviral activity[43].
1978	Elion and Schaeffer found ACV to be highly selective for herpes-like viruses, but is only slightly reactive against cytomegalovirus (CMV) (ref. 33, 43, 76 and G.B. Elion, personal communication).
1982	The FDA approved acyclovir for topical and intravenous clinical use.
1985	The FDA approved acyclovir for oral clinical use.
Ganciclovir	
1961	Julien Verheyden joined the newly formed Syntex Institute for Molecular Biology (SIMB) established by Joshua Lederberg and Carl Djerassi to explore the emerging field of molecular biology (ref. 45 and J.P. Verheyden, personal communication).
1963	Verheyden synthesized iodinated pyrimidine and purine nucleosides[45].
1969	J.G. Moffatt established the structure of nucleodin, a broad spectrum antibacterial and antitrypanosomal agent of natural origin[45].
1971	G. Owen of SIMB synthesized a nucleoside analogue of nucleodin[45,77,78].
1974	Verheyden's group synthesized a series of 4'-substituted purine and pyrimidine nucleosides, that were inactive in biological screens for antiviral, antibacterial, antitumor and antifungal properties (ref. 45 and J.P. Verheyden, personal communication).
1974	Syntex management redirected SIMB towards developing an aminoglycoside, without considerable productivity (J.P. Verheyden, personal communication).
1979	Acyclovir was demonstrated to be non-toxic at therapeutic doses[79].
1980	Verheyden's group synthesized and submitted ganciclovir for biological evaluation[45].
1983	Syntex became aware of the potent gonadal toxicity of ganciclovir, and decided to develop it for more limited indications[44].
1989	Ganciclovir was approved for the treatment of sight-threatening CMV.

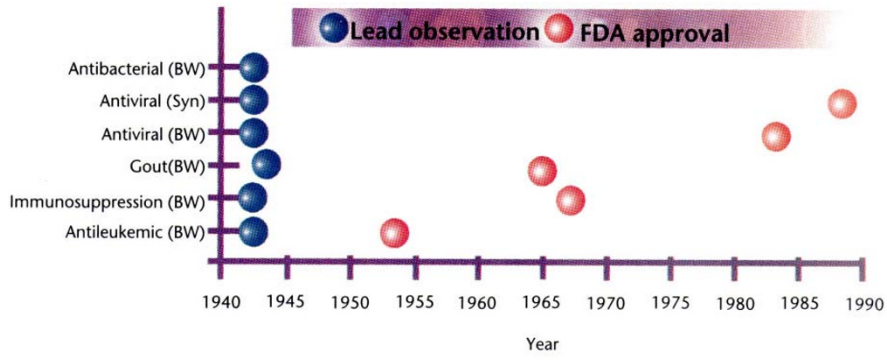

Fig. 1 Comparisons of the time required to develop purine analogue drugs. BW, Burroughs Wellcome; Syn, Syntex.

A standard but possibly superficial explanation for the differences in the time to new drug approval is that purine analogues simply are toxic drugs and priorities were systematically set to develop drugs first for the most severe conditions. Although the issue of toxicity is important when prioritizing the indications for the development of purine analogue drugs, infectious diseases in the 1940s had severe morbidity and mortality, and there were few therapies to alter their course. For instance, in 1942 penicillin had not yet been developed, and there were no efficacious antivirals. Thus, great medical and economic incentives existed for the development of any drug including purine analogues that could be used to treat these diseases. Furthermore, allopurinol was quickly discovered to have limited toxicity[13,14], yet its use in gout was remarkably delayed. The toxicity of these drugs should not have been sufficient to prevent high priority testing in all of the important diseases where they could have been applied. Moreover, careful examination of the events involved in the development process reveals that factors other than concern for toxicity substantially influenced the rate of drug development.

Hitchings' lead observations created a situation in which the opportunity arose to develop drugs simultaneously for a variety of seemingly unrelated clinical problems. Therefore, differences in the rate of drug development must be associated with factors other than limitations in the foresight of basic scientists[15]. When Hitchings' lead observations were published in 1950, sufficient clinical information existed for clinicians to predict the potential therapeutic benefits of purine analogues for each hypothesized indication[16–18]. In every case except the use of azathioprine for immunomodulation, relevant clinical data suggested that the pathogenesis of the disease would yield to the newly discovered drug. These data were available decades before Hitchings' findings were published. The case studies of pharmaceutical innovation at Burroughs Wellcome and Syntex suggest that the marked differences in the time required for drug development across indications arise because of differences in the transfer of information across the interface between basic scientists and external clinical researchers not in the transfer from basic scientists to the medical departments of the same company. The most important factor influencing the flow of information across this interface appears to have been the presence or absence of a clinical champion (see the Methods section for definition) who pulls the application of basic findings toward a particular treatment.

Clinical champions as determinants of rapid drug development

The development of 6-mercaptopurine (6-MP) was far faster than the average of 11 to 15 years that are now quoted as the time necessary to develop a new chemical entity. Examining the flow of information between Burroughs Wellcome and the Sloan-Kettering Institute and the roles that individuals performed in each of these organizations reveals factors that influenced the time required for drug development. Hitchings' group was permitted to pursue undirected research, because research and development (R&D) management was sympathetic to fundamental curiosity and science and was confident that the work would lead to useful outcomes for the company. Although Burroughs Wellcome had confidence in the science, no one in the medical group predicted or uncovered clinical applications for the work on purine analogues. Fortunately, Burroughs Wellcome permitted Hitchings and Elion to send their compounds to an external group to screen them for activities that might lead to clinical indications. Joseph Burchenal at Sloan-Kettering provided the clinical data that became integral to the discovery and development of 6-MP (ref. 12, 19–21). This occurred before the purine analogues had been evaluated by Burroughs Wellcome as chemotherapeutics. In fact, Charles F. Kettering hired two additional chemists to speed Burroughs Wellcome's research (G.B. Elion, personal communication) According to Gertrude Elion, it is likely that neither the medical department nor the marketing department at Burroughs Wellcome knew of their discovery until after the compound had demonstrated clinical utility in leukemic patients treated in the Sloan-Kettering trials (G.B. Elion, personal communication). Clearly, Hitchings and Elion were limited in all of their studies of purine analogues because few clinical researchers were allocated to their projects. However, this point that clinicians treating a particular disease and not the company producing the chemical entity may be the primary drivers of drug development is reinforced by each of the succeeding case studies.

As was the case for developing indications for 6-MP, the events in the development of azathioprine illustrate that rapid drug development is stimulated by open communication between industrial and academic settings and is very likely to be initiated by clinicians interested in discovery of new treatments for perplexing clinical problems. In this case, it appears that three physicians, Robert Schwartz, William Dameshek and Roy Calne, were critical to defining clinical applications for the compounds that *they* sought from Burroughs Wellcome[22–28]. The initial hypothesis for the use of azathioprine appears to have come largely from clinical investigators external to Burroughs Wellcome[23–28]. Although Hitchings' statement in 1950 generally included any clinical state in which target cells proliferated more rapidly than host tissues, immunosuppression was not originally considered by Hitchings or other members of the Biochemistry Department as an indication to pursue. Schwartz and Dameshek prompted the Biochemistry Department at Burroughs Wellcome to focus on immunosuppression, because

of their interest in autoimmune disease[22,24,25]. Later Calne requested that Burroughs Wellcome provide him with compounds to investigate how to prevent transplant rejection[23,26–29]. Once again, academic clinicians promoted the application of Hitchings' lead observation to clinical indications resulting in rapid drug development. The critical clinical insight for the development of azathioprine was Schwartz and Dameshek's hypothesis that drugs known to prevent rapid cell proliferation might serve as effective immunosuppressives[24,25]. According to Gertrude Elion, if Schwartz and Dameshek had not encouraged her group to develop an animal model for testing the immunosuppressive activity of purine analogue drugs, the Biochemistry Department at Burroughs Wellcome might not have pursued this indication (G.B. Elion, personal communication). Again the drive of clinical champions appears to have promoted drug development when internal resources were limited.

It is interesting and surprising that development of 6-MP and azathioprine was drawn out by outside clinicians, not by researchers or the medical department at Burroughs Wellcome. The company was not structured to transfer basic scientific observations into marketable drugs, because few clinical researchers were allocated to the small Biochemistry Department, and perhaps because Burroughs Wellcome lacked the expertise of clinicians with active practices and vested interests in treating diseases. Even more remarkable, Burroughs Wellcome did not identify the clinical champions; in each case, the outsiders approached Burroughs Wellcome for compounds to test. Hitchings' lead observation presented the researchers in the Biochemistry Department with the opportunity to develop purine analogues for several distinct indications, but they required outside help to effectively pursue these lines of research. They needed clinical investigators with intense interests in particular diseases in order to transfer their lead observations to useful drugs. These clinicians could actually transfer the scientific findings to innovations of clinical value, whereas the researchers inside the company could only enumerate some of the possibilities.

Although research on xanthine oxidase inhibitors began earlier than the work on azathioprine [ref. 12 and D.C. Lorz & G.H. Hitchings, Specificity of xanthine oxidase (Abstr.). Am. Chem. Soc., 1956; D.C. Lorz & G.H. Hitchings, Specificity of xanthine oxidase (Abstr.). Am. Soc. Biol. Chem., 1950] and the biochemical pathway of uric acid production and the role of hyperuricemia in gout were known in 1944 (ref. 12, 17), Burroughs Wellcome did not investigate the use of xanthine oxidase inhibitors for gout until R. Wayne Rundles noted decreased uric acid concentrations in a patient who received allopurinol to prolong the effects of 6-MP (ref. 32–34). Why was the clinical pull to explore the value of xanthine oxidase inhibitors delayed? Surely it could not be that their was no medical value or market for preventing acute gout attacks. In the 1950s physicians were intensely interested in the metabolic basis of disease. Other Burroughs Wellcome scientists pursued Hitchings' lead observation concerning the purines and pyrimidines[32–39]. What inhibited the timely investigation of the use of purine analogues for the treatment of gout?

Elion believes that clinicians may not have recognized the potential utility of purine analogues in the treatment of hyperuricemia because relatively few researchers were involved in the study of gout (G.B. Elion, personal communication). The findings of Elion's group might not have been well known to researchers in this area (G.B. Elion, personal communication),

Table 2 Selected correspondence between clinical investiagtors at Sandoz and basic scientists at Burroughs Wellcome

Borel, J.F. & Friedli, H. Letter to D. J. White. 15 November 1976.
Borel, J.F. & Friedli, H. Letter to D. J. White. 6 May 1976.
Borel, J.F. Letter to D. J. White. 3 February 1977.
Borel, J.F. Letter to D. J. White. 19 January 1977.
Borel, J.F. Letter to D. J. White. 15 June 1977.
White, D.J. Letter to J. F. Borel. 27 April 1976.
White, D.J. Letter to J. F. Borel. 21 May 1976.
White, D.J. Letter to J. F. Borel. 24 November 1976.
White, D.J. Letter to J. F. Borel. 3 November 1976.
White, D.J. Letter to J. F. Borel. 23 December 1977.
White, D.J. Letter to J. F. Borel. 27 January 1977.
White, D.J. Letter to J. F. Borel. 9 June 1977.
White, D.J. Letter to J. F. Borel. 14 September 1977.
White, D.J. Letter to J. F. Borel. 27 September 1977.
White, D.J. Letter to J. F. Borel. 5 September 1977.

but earlier studies of xanthine oxidase inhibition were clear [D.C. Lorz & G.H. Hitchings (Abstr.). Am. Chem. Soc., 1956, and (Abstr.). Am. Soc. Biol. Chem., 1950] and published[12]. During that time, fear of iatrogenic effects from xanthine oxidase inhibition may have stifled research. Researchers suggested that inhibition might induce xanthine oxidase and promote the accumulation of relatively insoluble precursors that could also produce crystals, both of which could exacerbate gout (G.B. Elion, personal communication). However, Elion's group performed experiments to address these fears, though these studies do not appear to have significantly sped development. The time required to develop allopurinol is intriguing because development was not delayed by the basic scientists within the company; Burroughs Wellcome produced the data supporting the potential for allopurinol's clinical application. What is fascinating is that in spite of the legitimacy of the hypothesis that was held by Burroughs Wellcome and their close relationship with physicians vitally interested in disease other than gout, their insight alone could not produce a drug to treat gout.

Hindsight permits us to speculate that a disease-oriented clinician (that is one intensely interested in arthritis and particularly gout) needed to emerge if the hypothesis was to be tested for this indication earlier than it was. [Rundles began collaborating with Burroughs Wellcome's biochemistry department in 1957, studying purine metabolism in patients with leukemia (G.B. Elion, personal communication).] Rundles did recognize the implications of decreasing uric acid concentrations in patients with chronic granulocytic leukemia (CGL) and did extrapolate them to other hyperuricemic states, but his suggestion to use the drug to treat gout was delayed many years. Often he had used the drug in patients with leukemia and noted its potent effects in lowering uric acid concentrations. No arthrologist appeared before he finally targeted gout for testing. He helped establish a tight loop between observations of xanthine oxidase inhibition *in vitro* and clinical applications of these findings, and thus promoted the development of allopurinol (G.B. Elion, personal communication). Elion's group did not differentiate between basic and applied research and followed the lead. Interestingly, none of the next 20 xanthine oxidase inhibitors that they tested was as effective as allopurinol (G.B. Elion, personal communication).

The development of a purine analogue as an antiviral was a

long and interrupted process. The Biochemistry Department discovered purine analogues with antiviral activity as early as 1947; however, the purine bases were considered too toxic to be generally useful (that is, they were inhibiting enzyme systems that were common to virus and humans)[40,41]. Testing stopped between 1949 and 1968 despite the early positive leads. In 1968, evidence had accrued that arabinosyladenine (Ara-A) inhibited DNA and RNA viruses and was much less toxic in humans because the effect was on virus-specific enzymes. This renewed Elion's interest in antivirals (ref. 42 and G.B. Elion, personal communication). In 1970, Howard Schaeffer synthesized acyclic purine nucleosides using methods that were entirely different from the work that Elion's group had been performing[29,39,43]. The acyclic nucleoside analogues preferentially inhibited viral DNA replication with less toxicity to host DNA (ref. 43). The impetus created by these basic science findings led to the development of acyclovir. Had Schaeffer or other researchers at Burroughs Wellcome been subjected to the clinical pull of the need for antivirals, perhaps the synthesis and testing of purine nucleoside would have occurred earlier.

In fact, the time required to develop acyclovir was short, from synthesis in 1974 to approval in 1981. Although structural differences exist between the compounds originally investigated and acyclovir, the major impediment to the development of an antiviral drug was fear of toxicity. Once this fear had been overcome by demonstration that related compounds such as Ara-A (ref. 42) had reasonable therapeutic indices, Burroughs Wellcome began research on 2,6-diaminopurine arabinosides. These were derivatives of the compounds that they had originally investigated in 1949 (ref. 40, 41).

The development of purine analogues as antivirals occurred much later in spite of the fact that Hitchings proposed and demonstrated antiviral activity as early as 1949 (ref. 11, 40, 41, 44 and G.B. Elion, personal communication). Obviously, the Biochemistry Department at Burroughs Wellcome cannot be faulted for "delaying" the development of an antiviral. It was a small laboratory in New York (and later North Carolina), separated from the virology laboratories in England. It had little clinical support and few basic scientists initially, and was actively engaged in the other research projects previously mentioned. Nevertheless, Hitching's lead observation opened the door for research on the antiviral properties of purine analogues, which proceeded outside of Burroughs Wellcome[34,35,42]. We propose that the lack of a clinical champion to drive development despite the fear of toxicity slowed development of purine analogues for this indication. Once this fear was overcome by the activities and engagement of basic scientists and clinicians inside of Burroughs Wellcome, and when John Bauer (most notably) became involved, the development of acyclovir proceeded rapidly. This case study serves as another example of drug development in which no clinician emerged early in the process to apply Burroughs Wellcome's compounds, and accentuates the critical role of clinical champions for rapid drug development. This fact is clearly illustrated in the example of similar research performed at Syntex.

The development of ganciclovir appears to have been slowed because available information on the potential clinical applications of purine analogues was not used by the company to direct the synthesis of new chemical entities. The Syntex Institute of Molecular Biology, a laboratory unit within Syntex, clearly focused on the synthesis of new compounds rather than on the discovery of compounds for a particular medical indication. By the time that they began their series of syntheses, sufficient data existed suggesting uses for purine and pyrimidine analogues (ref. 32–39, 45 and J.P. Verheyden, personal communication). However, SIMB was not structured to use its skilled chemists to translate the available information on the properties of purine analogues rapidly into useful chemotherapeutics. SIMB had no clinical leadership and no clinical expectations of it to guide the examination of novel compounds. Little interdisciplinary exchange seems to have occurred between the chemists and biologists or clinicians, and no broad connections were made between the structures of the nucleosides synthesized and a multitude of potential clinical indications for which they could be used (J.P. Verheyden, personal communication).

Julien Verheyden's ability to handle interdisciplinary resources, may have been one factor that ultimately allowed the group at Syntex to succeed in this highly competitive area. After the approval of acyclovir (ref. 45 and J.P. Verheyden, personal communication), Verheyden read much of the literature on viruses and investigated all compounds reported to have antiviral activity. However, Verheyden was primarily interested in chemistry, not in the application of nucleoside compounds to chemotherapeutics (ref. 45 and J.P. Verheyden, personal communication). Instead of being drawn into the clinic by perceived need, purine and pyrimidine analogues were slowly pushed through the stages of development by chemists from SIMB. Only after ganciclovir and its effects had been discovered, did Clyde Crumpacker and other clinicians finally demand its use for cytomegalovirus (CMV) retinitis (ref. 45-48 and J.P. Verheyden, personal communication). But why didn't Syntex seek Crumpacker earlier as a key member of the research team? Perhaps less time would have been required to develop ganciclovir had Syntex sought outside clinicians interested in antiviral therapy to aid in refining their compounds until they proved to be efficacious. It seems that, in this case, establishing relationships between basic scientists within the company and clinical investigators may have provided the opportunity to transfer compounds more rapidly from the laboratory to clinical practice. These bridges between basic science and medicine might function best if deliberately forged.

Discussion

By analyzing the significant events[10] that led to the development of five purine analogues discovered by scientists working at two companies, the authors have uncovered evidence that a critical and perhaps limiting factor in the application of compounds as useful therapeutic agents was the involvement of clinical investigators employed outside of the companies that ultimately marketed the drugs. Each clinical investigator (clinical champion) perceived that a basic science lead observation identified agents that could affect the pathophysiologic process of a disease in which he was interested, and pulled the development of a compound for that indication. The efforts of the Burchenal and C.P. Rhoads in the development of 6-MP, and Schwartz, Dameshek, and Calne in the case of azathioprine, indicate that the pull of an interested clinician can accelerate drug development even in instances when the pathophysiology of the disease is not completely understood. These case studies show that push by basic scientists or other industry professionals does not appear to be sufficient for rapid drug development. It is surprising that, in the case of 6-MP and

azathioprine, Burroughs Wellcome's priorities for development were set by researchers outside of the company. In the cases of allopurinol, acyclovir, and ganciclovir, when no clinician emerged as a strong advocate for new therapies, drug development times occurred long after the lead observation. In these last cases, the compounds were applied to their potential indications only after clinicians were drawn to this action by overwhelming preclinical data that could no longer be ignored or by serendipity.

After completing this study, the authors uncovered further evidence supporting the importance of clinical champions extending to today. Long after his work with Burroughs Wellcome, Roy Calne became intrigued by data suggesting that Sandoz had a compound, cyclosporin A, with immunosuppressive effects (see Table 2). In 1976, an associate of Calne's, David White, wrote to J.F. Borel of Sandoz requesting cyclosporin A to test in rat models. Note that the correspondence was initiated by Calne *not* Sandoz. Correspondence between White and Borel between May of 1976 and December of 1977 clearly demonstrate that Calne and White originated the idea and pushed for the development of cyclosporin for prevention of allograft rejection. Ultimately and with some reluctance on the part of Sandoz, Calne and White were given enough cyclosporin A to test its effects in their *in vitro* assays of allograft rejection, and in *in vivo* studies of rat and porcine heart graft survival. They ultimately demonstrated that cyclosporin was useful for preventing allograft rejection[49–52]. This evidence suggests that in spite of his overt role as a clinical champion for the development of immunosuppressives for use in transplantation, Sandoz did not identify Calne as a champion for drug development and seek him out to promote the development of cyclosporin. Industry even today did not have the wisdom to seek Calne's help — probably because they did not conceive of the indication themselves, or investigate his prolific track record of publications on immunosuppression. The process by which purine analogue drugs were developed is only one of several pathways to drug development. However, Calne's role in the development of cyclosporin suggests that clinical champions may be equally important in other routes of drug development.

Our study offers insight concerning the management of information in drug development. The development of drugs of various chemotherapeutic classes from research on purine analogues has demonstrated several principles about the nature of medical technology transfer and raised a series of new questions. First, this study demonstrates that a circumscribed lead observation potentiated the development of drugs for use in cases of leukemia, immunosuppression, gout, and viral disease. However, it appears that the identification of targets and biochemical pathways by the basic scientists was not sufficient to promote rapid drug development. The time required to develop the purine analogue drugs illustrates that the rate at which technological innovations occur is not entirely or even substantially dictated by the scientific knowledge base or by traditionally cited methods for setting research priorities. These variations in the rate of innovation are related to one important yet misunderstood and probably underappreciated factor: the presence or absence of a clinical champion who is charged with managing the disease and therefore is likely to reside outside of the industry.

The conclusions drawn from these case studies of innovation at Burroughs Wellcome and Syntex appear to be applicable to the modern era of rational drug discovery. The collection of case studies of drug development spans nearly five decades from the early 1940s to the late 1980s. Furthermore, the evidence suggests that Calne served as a clinical champion in the recent development of cyclosporin. Although the tools and techniques available for drug discovery and development have improved over time, these case studies illustrate that the presence of a clinical champion continues to be an important determinant of the time required for drug development.

Though relatively few studies have focused on the roles of individuals in drug development, champions have been identified as important influences on the success of innovations in other industries[9,10,53–62]. Champions have been shown to determine the objectives and goals for a project and play a dominant role in overcoming technical and organizational obstacles, primarily by getting R&D management sufficiently interested in the project[53,54,60,61]. Champions identify relevant scientific data, maintain strong connections in their domain of expertise and with external sources of information, and effectively translate between the two systems[7,9,10,53,54,60–62]. The clinical champions described in this study differ from champions in other industries in that they are academic investigators external to the company that ultimately marketed the drugs.

Samuel O. Thier proposes that without clinical investigators "the relevant scientific questions that feedback into the biomedical system will not be asked"[63]. This seems to be precisely the case in the slow development of allopurinol, acyclovir and ganciclovir. Thier stresses the need to develop clinical investigators versed in the "integrative" sciences to connect fundamental observations to clinical problems[63]. An Institute of Medicine committee found that this role for clinicians is infrequently acknowledged, encouraged, or supported, but appears to be crucial to the development of novel diagnostic and therapeutic modalities[64]. Although ignoring the importance of clinical champions does not necessarily prevent successful development as these cases show, it can be a significant impediment in situations in which time to market is crucial.

Rebecca M. Henderson has shown that the most successful pharmaceutical companies of the 1990s achieved competitive advantage by enhancing their abilities to innovate in information-intensive environments through tight connections to the larger scientific and clinical communities and to allocate resources effectively in order to stimulate rapid transfer of information[65,66]. These pharmaceutical firms are characterized by their constant attention to the integration of knowledge across disciplinary and organizational boundaries, and their ability to continually reexamine the possible linkages between relevant scientific and medical disciplines[65]. This idea that information flow across disciplinary boundaries is essential to scientific problem solving is widespread in the literature on effective management of research-based organizations[54].

If indeed the presence of a clinical champion promotes more rapid drug development, can champions be deliberately sought, trained, and placed in positions to promote drug development? Most of the functions of clinical champions appear to be ingrained in the traditional training of clinician-investigators in academic health centers. However, their roles in promoting and detecting fundamental investigation and as drivers of the technology transfer process distinguish the clinical champion from other clinical investigators. These roles are rarely encouraged or taught in traditional academic settings. Therefore, although many clinician-investigators are posi-

tioned to serve as clinical champions, most do not. In order for this role to become more commonplace, the functions of clinical champions must be appreciated and encouraged, and the skills necessary to transfer enabling scientific observations to clinical applications must be taught. Attention to the fact that clinical champions exist, as well as increased awareness of their value as critical factors in drug development, may encourage more clinicians to seek this role.

The focus on clinical management is the key feature that distinguishes clinical champions from physicians who work within the pharmaceutical industry. In these case studies, this focus appears to drive certain clinicians to make connections between basic science findings and clinical indications, and to pull drugs into development. Physicians inside of pharmaceutical companies are not continually presented with patients' problems, which, for the clinical champions in our study, provide the impetus for promoting rapid drug development. Clinical champions appear to accelerate pharmaceutical innovation, by defining and vigorously exploring novel targets for compounds with known apparent mechanisms of action. However, clinical investigators do not routinely function in this capacity. It may seem gratuitous but it appears necessary to say that to reduce drug development time pharmaceutical companies should attract and develop relationships with clinicians who demonstrate vision for improving the management of disease. Future research on the process of integrating basic and clinical information in drug development and on the role of the clinical champion may elucidate criteria for training researchers to perform this role.

Methods

The authors reviewed the literature on the factors (including organization and information management methods) demonstrated to have influenced drug development. Focusing on the development of purine analogues, we reviewed 205 articles covering the research leading to the development of 6-mercaptopurine, azathioprine, allopurinol, acyclovir and ganciclovir. Data concerning the development of pyrimidine analogues such as trimethoprim were excluded from this study. The authors interviewed Gertrude Elion and Julien Verheyden of Syntex to verify or refute findings drawn from the literature, and to provide additional information that could not be gleaned from the literature. All sources were used to detail the basic science and clinical knowledge possessed by the researchers at specific times in the development process.

The literature was subjected to three analyses: (1) identification of all significant events[28] (2) identification of the lead observation (as defined below) for the development of each drug, and (3) examination of the roles of individuals and organizational structures that influenced the time required for drug development. All facts were verified in interviews with Elion and Verheyden. Elion also read and critiqued our accounting of the facts. But the interpretation of those facts is the responsibility of the authors. The data collected, the literature and the interviews were used to construct chronologies of the innovative process at Burroughs Wellcome and Syntex between 1940 and 1988. Apparent inconsistencies within the case histories were examined and reconciled through interviews. Since research findings often are published up to several years after the studies have been completed, the dates when research findings occurred that are reported in review articles, symposia proceedings, and interviews were used to mark the start and completion of events. When these data were unavailable, the dates by which findings were published were used and noted. The approximate dates at which significant events were determined to occur were compared for each case study.

The second part of this analysis involved determining the existence of one particular type of significant event, the lead observation. A lead observation is a decisive event[10] that creates the opportunity for existing basic science knowledge to be applied to a specific clinical indication. This opportunity can arise, even if an innovation is not immediately envisioned. A lead observation is a form of recognition of scientific opportunity[10] that motivates the acquisition of new fundamental knowledge to promote innovation. When the lead observation exists, it defines the earliest point of origin of the drug development process. A lead observation was determined to exist if it met three criteria: (1) It was a basic science discovery or finding; (2) it preceded the clinical application discussed; and (3) it created the potential for applying existing basic science knowledge to clinical disease states.

The authors examined the case histories to identify individual roles and organizational structures (as defined by the literature review of organization and information management) that might be associated with reducing or increasing the time required for drug development. The authors identified clinicians who served as champions[9,10,53–62]. as critical factors in the drug development process, as we sought to further define this role.

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