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The Cancer Chemotherapy National Service Center: Development of an Innovation System

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Abstract

This article frames the historical record concerning the activities of the Cancer Chemotherapy National Service Center as an illustration of the US government's role in the development of structural and functional features of an embryonic technological innovation system. While the Center's contribution to the development of pioneering cancer drugs has long been recognized, the article highlights how the Center promoted the cooperative participation of a growing number of individuals and organizations in the search for effective chemotherapeutic cancer treatments. Such participation accelerated the development and diffusion of knowledge related to the anticancer properties of large numbers of substances and compounds, as well as to protocols and methods for pre-clinical and clinical testing whose use later became common features of the cancer chemotherapy innovation system.

JEL Classifications: H59, O38.

Keywords: cancer chemotherapy, innovation system, entrepreneurial state.

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Introduction

The Cancer Chemotherapy National Service Center (henceforth, CCNSC) was an organization created by the US government in 1955 for the management of the Cancer Chemotherapy Program (henceforth, CCP or Program). The Program marked a substantial increase in the government's financial commitments to cancer-related research, a first step along the path that led in 1971 to the National Cancer Act and the beginning of the war on cancer. Understandably, in light of the magnitude of the investments involved, the literature evaluating these government programs has been primarily concerned with identifying the number of commercially available anticancer drugs that resulted from them.¹ This approach is consistent with contemporary views of the general role of public research in the US pharmaceutical innovation system—seeding private-sector drug development efforts by funding biomedical research and early-stage pre-clinical studies.

Although cancer was becoming an increasingly prominent cause of mortality in the years following World War Two, the CCNSC came into existence at a time when the effectiveness of chemotherapeutic treatment of cancer was unproven, and its promise hotly contested: a time when an innovation system focused on cancer chemotherapy was not in place. Active lobbying of government by non-profit organizations and promising results from early screening programs provided the impetus for scaling up public investment in the field. Accordingly, this article revisits the historical evidence concerning the activities of the CCNSC, and focuses on the following research question: how did the CCNSC contribute to the development of structural and functional features of an embryonic technological innovation system focused on cancer chemotherapy? Drawing from an extensive literature on the activities of the CCNSC, including contributions from many scientists directly involved in the design and implementation of the CCP, the article examines the role of the CCNSC in various processes that characterize the evolutionary development of an innovation system. It finds that the CCNSC played a critical role in: (a) scaling up the development and diffusion of knowledge, practices, and resource bases relevant to cancer chemotherapy; (b) promoting the growth of specialized organizations and the cooperative participation of scientists and pharmaceutical firms to the search for cancer treatments; and (c) seeding the interactions among key actors that are the hallmark of an active innovation system.

The system of innovation framework adopted in this article highlights features of the CCNSC that make it a distinctive and original institution among those created by the federal government during the post-World War Two decades. The CCNSC did not only fund costly and high-risk research activities, but also played an active and coordinating role in the organization of pre-clinical and clinical research, becoming *de facto* the central node of an innovation network encompassing academic researchers, suppliers of research tools, testing laboratories and clinical trial sites and participants. It represents therefore an illustration of government programs instituted post-World War Two whose remit went beyond providing financial support to scientific research through grants or to innovative enterprises through procurement contracts.²

¹ By this standard, the CCP managed by CCNSC was the origin of virtually all available treatments for several decades: “When he was Director of the NCI, Vince DeVita was often asked how many drugs came out of the program. The answer is, up until 1990, all of them ...” (Vincent T. DeVita Jr. and Edward Chu 2008, 8647). Even then, whether or not the war on cancer was a successful government initiative continues to be hotly debated (DeVita and Elizabeth DeVita-Raeburn 2016; Clifton Leaf 2014).

² While it is common to identify in the recommendations made by Vannevar Bush (1945) the inspiration for government-sponsored research, Bhaven Sampat (2012) casts a broader perspective on the history of the National Institutes of Health as an actor balancing the goal of support to scientific research with more specific health-related missions. Sampat and Kenneth Shadlen (2021) reflect on

The article draws inspiration from and contributes to the scholarship on the role played by the US government in the development of innovative industry sectors of the post-World War Two economy, and its interactions with private actors. As discussed further in the next section, much of this literature conceptualizes the innovative performance of regions, sectors, and national economies as the result of activities carried out in interaction by various actors, who together constitute an innovation system (Christopher Freeman 1987; Bengt-Ake Lundvall 1992; and Richard R. Nelson 1993). Within this literature, it has been increasingly recognized that public-sector institutions and programs have often been instrumental to promoting organizational learning and institutional changes enabling the development of effective innovation systems. Thus, William H. Janeway (2018) argues that the venture capital industry's involvement with the rise of Silicon Valley firms in the field of information and communication technologies built upon earlier initiatives promoted by the Department of Defense, especially through its Defense Advanced Research Project Agency. Mariana Mazzucato and Douglas Robinson (2018) examine the history and current changes in the role of the National Aeronautics and Space Agency in the evolution of the Low-Earth Orbit innovation system. More broadly, Mazzucato (2013) argues that the US government's role in the innovation process cannot be characterized exclusively as remedying market failures. She claims instead that US government action has on repeated occasions been instrumental to creating the pre-conditions for private investment and ultimately the creation of markets for many important new technologies. The experience of the CCNSC represents arguably an instance of the government activities that Mazzucato considers a hallmark of an *entrepreneurial state*.

The next section of the article will provide an overview of the system of innovation framework, identifying key functions of a technology innovation system that will serve as the lens through which the historical evidence will be organized in the article. Before delving into the characteristics of the CCP and of the CCNSC, two sections will briefly sketch their historical context. The first will discuss the rising prominence of cancer as a cause of mortality in the post-World War Two period, as well as the impetus for greater financial support to cancer-related research. The second will discuss the transformation of pharmaceutical research and development (R&D) activities taking place since the 1930s and its manifestation in the area of cancer chemotherapy. After taking stock of the main obstacles to the scaling up of the search for anticancer drugs around 1950, the article will turn to a discussion of the CCP and of the CCNSC. The focus will be on activities of the CCNSC related to the development of key functions of an innovation system, with special emphasis on the development of research methods and on institutional policies about intellectual property rights (IPR) that greatly influenced the interactions between the Program and the pharmaceutical industry.

The Innovation System Framework

The origins of the innovation system framework can be traced to a handful of monographs and journal articles, including Freeman (1987), Lundvall (1992), and Nelson (1993). While these early writings focused largely on national specificities of the innovation system, later work has adapted the system framework to the study of innovation in economic regions and to the study of innovation in specific areas of technology or specific sectors.³ A common thread across

the US government's response to the COVID-19 pandemic, noting how public funding in this case was directed to late-stage product development and manufacturing.

³ Early contributions to a now sizeable literature on "regional innovation systems" include Philip Cooke, Mikel G. Uranga and Goio Etxebarria (1997), Jeremy Howells (1999) and AnnaLee Saxenian (1994). Bo Carlsson's writings pioneered the use of the concept of a technological innovation system (Carlsson and Rikard Stankiewicz 1991), whereas Franco Malerba and his co-authors proposed a sectoral system perspective on innovation (Stefano Breschi and Malerba 1997; Malerba and Luigi

these literatures is the belief that innovation is a process resulting from the interactions of multiple actors leading to the development and diffusion of new products or processes (Lundvall 1992).⁴ While some studies of innovation systems focus on what we may call *mature* systems, others study the development of an innovation system—a dynamic perspective more closely aligned with the subject of this article.

Studying an evolving innovation system requires identifying the emergence of structural components of the technological innovation system (actors, networks, and institutions), and examining how they contributed to the organization of key processes of the system, what Anna Bergek, Staffan Jacobsson, Bo Carlsson, Sven Lindmark, and Annika Rickne (2008) refer to as its *functions*. These processes include: (a) the development and diffusion of knowledge within the system; (b) influences on the direction of search; (c) entrepreneurial experimentation; (d) market formation; (e) legitimation; and (f) resource mobilization. In a mature technological innovation system, the organization of such processes is relatively stable in terms of the role of different actors and their interaction patterns. But in a new system, the identity and role of participating actors is in flux, as are their interactions, and the different system functions are likely to develop at different times and in poorly coordinated fashion.

The innovation system perspective promotes a greater appreciation for the different ways in which government policy and public-sector institutions can influence innovation processes in a particular sector or technology area.⁵ In particular, it has been observed that the role of government evolves with the system of innovation, as the latter goes from its embryonic stage to maturity (Gil Avnimelech and Morris Teubal 2008; J. Stanley Metcalfe 1993; Teubal 1997). This perspective is germane to this article's focus on an early phase of the US government's involvement with cancer chemotherapy research. The 1955 launch of the CCP followed the creation of the National Cancer Institute (NCI) in 1937 as a specialized institute focused on cancer-related research and practices. In turn, the CCP was a precursor to the National Cancer Act of 1971, the legislative act that marks the beginning of the "war on cancer".

Later sections of the article will discuss the contributions made by the CCNSC to the development of various functions of the technological innovation system of cancer chemotherapy. It will be argued that the CCNSC's role was especially important in the development and diffusion of knowledge related to methods and procedures for pre-clinical and clinical research and the mobilization of resources dispersed among many actors. The CCNSC functioned as the central node of a decentralized drug development effort, enabling the scaling up of actors and the development of patterns of interactions amongst them.

Disease Burden Associated with Cancer

The increased public interest in chemotherapy as an approach to managing or curing cancers in the aftermath of World War Two reflected both the rising importance of cancer as a cause of death and the enthusiasm for chemotherapeutic approaches to the treatment of disease raised by pharmaceutical progress in other areas—most notably antibiotics. Since the mid-1930s cancer had established itself as the second leading cause of death in the US,

Orsenigo 1995; Malerba 2004). Recent analyses of the evolution of the literature on innovation systems are in Jan Fagerberg and Bart Verspagen (2009) and Souzanchi Kashani and Saeed Roshani (2019).

⁴ The emphasis on interaction is also an aspect of the "triple helix" framework proposed by Henry Etzkowitz and Loet Leydesdorff (2000).

⁵ Vivien Walsh and Muriel LeRoux (2004) provides a fascinating comparative account of the influences that features of the respective national innovation system had on the development of two anticancer drugs in the US and France—taxol and taxotère. While their research—and their consideration of the innovation system perspective—is closely related to that presented here, the emphasis in this article is on the evolution of the US innovation system in the broader technology area of cancer chemotherapy.

accounting for nearly 14.5 percent of all deaths in 1950 (Forrest E. Linder and Robert D. Grove 1947, 234) up from 8.6 percent in 1930 (Robert D. Grove and Alice M. Hetzel 1968, 393).

While long term improvements in health and life expectancy are the result of the complex interplay between economic progress and advances in the fields of public health and medical knowledge, the successful development of pharmaceutical drugs addressing bacterial infections (sulfa drugs, penicillin, and progressively additional classes of antibiotics) during the 1930s and 1940s drew renewed confidence in the possibilities of pharmaceutical treatment of additional human diseases and illnesses.⁶ Advances in medicinal drugs were claimed to have played a very important role in increasing US life expectancy from 65 to 70 years during the decade 1948-1958 (Francis C. Brown 1962). The president of the Pharmaceutical Manufacturer Association could boast in 1960 that modern drugs had contributed to reducing the death rates for afflictions like pneumonia, influenza, tuberculosis and gastritis, accounting for one third of deaths in the 1930s. While the role of pharmaceutical innovations may have been overstated, progress in reducing mortality due to diseases like pneumonia, influenza, and tuberculosis, ensured that other diseases—for which incidentally advances in chemotherapeutic treatment had been slow or even absent—became increasingly prevalent causes of death.⁷

Heart disease, stroke, and malignant neoplasms (cancer) were considered the three leading causes of death from disease at the end of the 1950. With respect to cancer, the vice-president of a leading firm characterized the industry's ability to treat cancer as poor, while effectively admitting the absence of any curative chemotherapy (Mortimer J. Fox Jr. 1959). It was estimated in 1966 that nearly 600,000 new cases of cancer would be diagnosed for the year, and that 300,000 would die with cancer (820 persons per day), accounting for one of every six deaths from all causes in the United States (C. Gordon Zubrod, Saul A. Schepartz, Joseph Leiter, Kenneth M. Endicott, Louis M. Carrese, and Carl G. Baker 1966, 462).

Just as important from the viewpoint of this article is to comment on the ongoing changes in the form of public support for biomedical research. While private foundations had played a central role in providing financial support for such research from earlier times, the postwar period witnessed both the scaling up of these investments and a strategic reorientation towards lobbying for government funding. While these developments were not exclusively concerned with it, cancer-related research was the focus of both. Thus, the establishment of the Sloan-Kettering Institute (henceforth, SKI) was the result of a \$4 million dollar donation by Alfred Sloan (Robert F. Bud 1978), and a seismic shift occurred in the activities of the American Association for the Control of Cancer when health activist and philanthropist Mary Lasker joined its Board and transformed it into the American Cancer Society in 1944. Lasker undertook to increase the society's budget to not only provide continuing financial support to cancer research but also organize a strong lobbying effort with the US Congress aimed at vastly increasing government support for the same (Michel P. Coleman 2013; Robert Cook-Degan and Michael McGeary 2006; Stephen P. Strickland 1972).

⁶ The relative significance of economic progress as opposed to advances in public health or medicine as determinants of the demographic transition, improved health conditions, and higher life expectancy, is the focus of a debate that erupted in the 1970s around "McKeown's thesis" (James Colgrove 2002; Thomas McKeown 1976; Simon Szreter 2002). The timing of these controversies is an important reminder that the enthusiasm for medical and pharmaceutical advances that dominated the early post-war period had cooled substantially by the 1970s. McKeown's thesis resonated with the much more critical view of the medical-pharmaceutical complex that dominated public discourse then.

⁷ The mortality rate for pneumonia and influenza had fallen by 68 percent, and that for infections of the gastro-intestinal organs by 82 percent. In an even shorter window of time, the death rate from tuberculosis fell by 80 percent between 1944 and 1957, and those for whooping cough, scarlet fever and diphtheria had fallen by more than 90 percent (Austin Smith 1960).

These developments mark a watershed moment in the history of cancer-related research. The growing demand for treatments and cures of at least the most frequent forms of cancer had been a factor in the creation of the NCI. But the pace of progress in the treatment of *most types of cancers* had been slow due to the poor conditions of technological opportunity.⁸ Advances had been hampered by the inability to identify common characteristics among its different types, obstructing the design of a common therapeutic strategy. The heterogeneous character of cancer had important implications in terms of the prospects of available treatments.

Since early in the century, surgical and—later—radiation approaches had been the mainstays of cancer treatment. They achieved moderate success only in localized forms of neoplasms, which could be excised or killed, but were largely ineffective against diffuse forms of cancer and against the distant spread of the disease from its original site. This left a large unmet demand for the treatment and cure of many cancer forms that chemotherapy could target. Yet, the idea that cancer could be treated through chemotherapy was rather radical as late as the 1940s.⁹ Renewed interest in cancer chemotherapy was stimulated by the results of research on the therapeutic effects of mustard gases occasioned by the observation during World War Two that exposure to sulfur mustards affected the bone marrow and lymph nodes of servicemen. Based on this evidence, the US Office of Scientific Research and Development sponsored a research project about the antitumor properties of nitrogen mustards directed by two pharmacologists—Alfred Gilman and Louis Goodman—at Yale University.¹⁰

The Evolving Nature of Pharmaceutical R&D in the Postwar Period

The foregoing discussion suggests that a confluence of factors set the stage for the qualitative changes in the nature and intensity of the research effort targeting the treatment of cancer that will be the focus of this section of the article. If trends in mortality rates and the rising influence of advocates for medical research pushed the treatment of cancer up the hierarchy of perceived biomedical priorities, ongoing and broader changes in the nature of R&D activities in the pharmaceutical industry framed the characteristics of the processes according to which these priorities were addressed.

The 1930s and 1940s marked extraordinary changes in the pharmaceutical industry. Key discoveries like the sulfonamides, penicillin, and development of effective mass-production methods heralded the transformation of the pharmaceutical business into a highly research-intensive industry sector (Alfred D. Chandler Jr. 2005; Louis Galambos and Jeffrey L. Sturchio 1996; Alfonso Gambardella 1995).¹¹ The R&D activities undertaken by the

⁸ The emphasis in this sentence reflects the fact that cancer is a term used to refer to a variety of different neoplastic diseases, at least one hundred according to Zubrod (1972). Cancer was described by Michael B. Shimkin (1961) as a class of diseases with “distinct etiologies, pathogenetic stages, and, probably, distinct intracellular and subcellular mechanisms and reactions” (Shimkin 1961, 861). Lacking knowledge of common denominators, each type of cancer was treated as a “separate disease” (Zubrod 1972, 1042).

⁹ After the development of early murine models of human tumors in the 1910s, a small number of research efforts were undertaken in Britain, Germany, and the US, whose objective was to screen classes of compounds for their effects on tumor growth (Angelika Burger and Heinz-Herbert Fiebig 2014), but hardly any culminated in clinical tests. Even more important, the clinical testing of the two drugs identified by these research efforts had to be suspended due to their toxicity (DeVita and Chu 2008).

¹⁰ It is also worth noting that the pursuit of a chemotherapeutic approach to the control of cancer became a rather distinctive feature of the efforts at controlling cancer in the US. The divergence between the US and other countries—most notably, Britain—is discussed as an instance of path-dependent development of treatment modalities in an essay by John Pickstone (2007).

¹¹ In particular, the discovery of penicillin and the US government-funded development of industrial production techniques marked a significant improvement in the conditions of technological

pharmaceutical firms that led this transition were mostly organized around the large-scale screening of substances for their therapeutic effects.¹² Among the firms that led this transformation of the pharmaceutical business, R&D capabilities were generally specialized in specific areas of disease. While research-oriented firms accumulated vast libraries of natural substances and synthetic molecules, conditions of technological opportunity differed greatly among areas of disease. Such differences reflected possibilities for effective in vitro or in vivo experimentation, the state of knowledge about specific therapeutic targets, and the prospective challenges of extrapolating results from the experimental or pre-clinical setting to the clinical.

Postwar research on the effectiveness of chemotherapeutic approaches to the treatment of cancer was based also on screening substances, both natural and synthetic, for later clinical tests (Bud 1978). But unlike or more so than other areas of biomedical research, screening activities in the areas of cancer chemotherapy faced considerable challenges. In a 1946 essay published in *The American Scientist*, Peyton Rous—winner of the 1966 Nobel Prize in Medicine—denounced the situation as follows:

At the present day a deplorably small proportion of the men who study tumors are engaged in the search for agents which will destroy them selectively. There is a compelling social reason for this state of affairs. Anyone venturing into the field of tumor therapy stakes both his scientific and his personal future against colossal odds, all past experience going to show that he may make thousands of tests and be left in the end with nothing, not even a tenuous idea of how to proceed. (Rous 1946, 335)

Rous's words reflected the modest results of screening efforts undertaken until then. One such effort was a screening program organized by Murray Shear in 1935 at the Office of Cancer Investigation of the Public Health Service.¹³ Shear's screening program was terminated in 1953 after more than 3,000 chemicals and hundreds of plant extracts had been tested for producing the necrosis of tumors (Zubrod et al. 1966, 350). The program used a single transplanted tumor model in mice, Sarcoma 37 (henceforth, S37), in order to test the anticancer properties of substances purchased in the open market or donated to it by third parties. At the termination of this screening program, only two substances had progressed to clinical testing.

The modest results of Shear's program did not deter other organizations from joining the quest thanks to the financial support of either private-sector philanthropists or public-sector programs. Among the former was the screening program launched in 1947 by the SKI. This had been established in 1945, ostensibly to bring the organizational techniques of contemporary industrial R&D labs to bear on cancer-related research (Bud 1978, 433). By design, the SKI was linked to the Memorial Hospital in New York so that the research process could transition from pre-clinical to clinical studies. This organizational feature promised to be

opportunity for innovation in the area of antibacterial chemotherapy and effectively launched the industry's "Golden Age" (Malerba and Orsenigo 2015). Not all pharmaceutical firms embraced the transition to the R&D-intensive business strategy described here—some focused increasingly on imitation and price competition as central aspects of their business strategy (Chandler 2005; Jeho Lee 2003).

¹² Screening techniques were not altogether novel, their use having been pioneered by Paul Ehrlich early in the twentieth century. What was novel was the scaling up of the screening efforts in areas of disease where appropriate techniques could be developed and the broadening of the efforts to identify substances that could be screened (Frederick M. Scherer 2010).

¹³ This Office and the Laboratory of Pharmacology of the National Institutes of Health were combined into the NCI two years later.

important given that the lack of effective linkages between pre-clinical screening and clinical testing was later identified as a critical weakness of Shear's program (Zubrod et al. 1966, 350).

The direction of the program was placed in the hands of Cornelius Rhoads, who had directed the Chemical Warfare Services of the US Army during World War Two, coordinating the scientific work on the antitumor effects of mustard gases. Rhoads organized the largest screening operation to date, setting up organizational ties with a variety of other institutional actors that submitted substances to the SKI for evaluation (Bud 1978, 443). The SKI not only offered to screen under conditions of confidentiality substances submitted by interested business firms, universities, research centers, and individual medical researchers. It also funded external research projects aimed at the development of promising compounds, as for example the research on purines carried out by George Hitchings and Gertrude Elion at the laboratory of Burroughs Wellcome USA (*ibid.*, 444).

The contribution of this screening program to the early development of anticancer drugs was substantial.¹⁴ By 1960, the SKI screening program had evaluated around 19,000 synthetic compounds and 19,500 materials of natural origin. Fourteen compounds had been found to lead to a marked inhibition of tumors in the primary screen used in the program, the murine S180 model (C. Chester Stock, Donald A. Clarke, Frederick S. Philips, and Ralph K. Barclay 1960, 3). Another 300 compounds had produced a slight inhibition of the tumors. Clinical testing of promising compounds identified in the SKI screening program was carried out at Memorial Hospital in New York. For three of the nine anticancer drugs discovered before 1955, the SKI was the institution where their antitumor properties were first identified.

Two of these drugs (6-Mercaptopurine and Thioguanine) had been developed in collaboration with Hitchings and Elion at Burroughs Wellcome. The other was a compound synthesized at the Lederle Division of American Cyanamid. These two companies led the industry in terms of their interaction with the major centers of cancer chemotherapeutic research. But the number of firms that contributed or used the screening facilities provided by the SKI was much larger, including Parke & Davis, Merck Sharp & Dohme, Lilly Research Laboratories, Smith Kline and French, Upjohn, Bristol, Abbott, and many others. Chemical firms, medical scientists, university laboratories in the US and abroad, are among the other entities that supplied the SKI with its raw material, compounds and natural substances for testing.

The early results of the programs at the SKI and of similar initiatives elsewhere were encouraging for some, and disappointing for others.¹⁵ While the former advocated for a more substantial effort aimed at screening drugs, the latter considered the hope for a chemotherapeutic approach to the cure of cancer to be misplaced. As the initial enthusiasm about the remission rates experienced by trial participants gave way to disappointment when tumors recurred and spread, critics of the approach maintained that too little was known about the etiology and pathogenesis of most cancers for any screening effort to have a chance at success.

Bottlenecks in the Expansion of Cancer Chemotherapeutic Research

At the dawn of the 1950s the innovation system focused on the development of cancer chemotherapies can be fairly characterized as operating in embryonic form. The major screening programs at the SKI and Chester Beatty Institute had created a template for

¹⁴ The SKI was estimated to account for 75 percent of the country's screening capacity around 1955 (Zubrod et al. 1966, 351).

¹⁵ Among the other screening programs, mention should be made of the program at the London-based Chester Beatty Laboratories, whose scientists made important early contributions to the study of derivatives of nitrogen mustards effective in the treatment of Hodgkins' disease and chronic leukemias (Walter Sneader 2005).

research that influenced future developments. While the prospects for treatment or cure of most forms of cancer were still dim by the early 1950s, the development of a small number of anticancer drugs on the basis of the existing screening programs fueled the growth of lobbying efforts aimed at increasing the US Congress’s financial commitments to cancer-related research. Such commitments—part of a broader increase in the volume of public-sector financial resources directed towards biomedical research (Sampat 2012)—were especially significant given the limited investment in cancer-related research by private firms.

While US government funding increased in both absolute terms and as a percentage of total research funding across all fields of research, the trend was amplified in the field of medical research where the US government share increased from 7 to 42 percent between 1941 and 1952 (see Table 1). Over that same time period, industry’s share of medical research fell from 55 to 35 percent, and that of philanthropic organizations from 27 to 14 percent (Irving Ladimer 1954, 114).¹⁶ It should be noted further that in contrast with other areas of research where it performed research funded by other sources, industry was not a net recipient of research funds in the medical field. Non-profit organizations accounted for around 50 percent of all medical research performed, and government laboratories for the remaining one-fifth (ibid., 116). This pattern of research performance was the result of the increasingly prominent role of the federal government as a sponsor of medical research, and of the changing balance between intramural and extramural research activities sponsored by the government, or more specifically by the Department of Health, Education and Welfare (henceforth, DHEW), and the Department of Defense which together accounted for more than 80 percent of federal spending on medical research. Almost all of the funds for extramural research activities were allocated to non-profit organizations (ibid., 118).

Table 1

Medical Research Expenditure by Sector, selected years (millions of dollars and percent of the total)

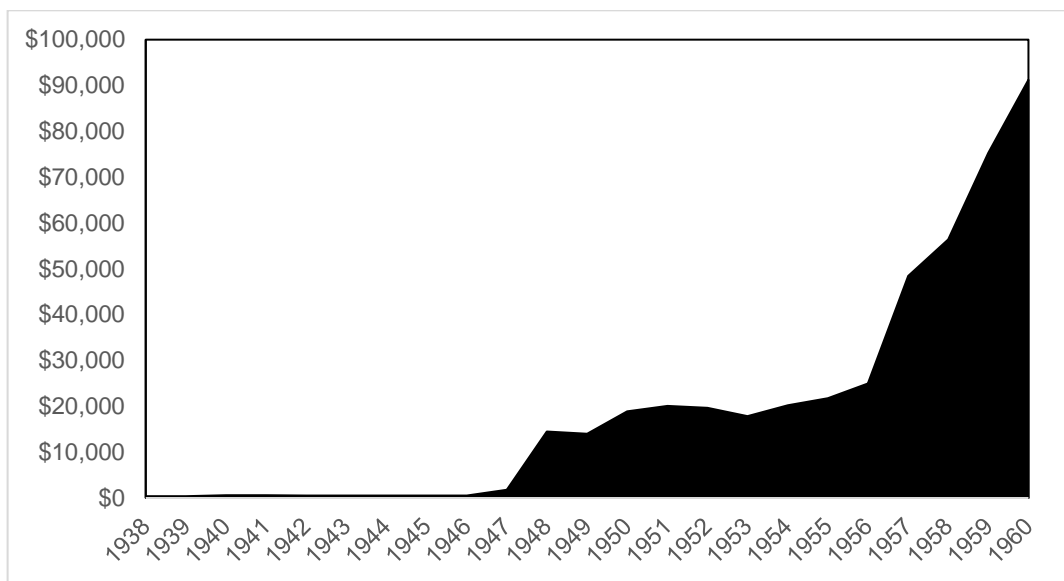
	Government		Industry		Philanthropy		Other Non-Profit		Total
	\$m	%	\$m	%	\$m	%	\$m	%	\$m
1941	3	7	25	55	12	27	5	11	45
1947	28	32	35	40	15	17	10	11	88
1952	73	42	60	35	25	14	15	9	173

Source: Ladimer (1954, 114)

Funding for cancer-related research had been relatively stable at a modest level since the creation of the NCI, but started growing in 1947. Congressional appropriations for the NCI grew from just above half a million dollars at the end of World War Two to nearly \$19 million in 1950. As Figure 1 shows, funding for cancer-related research grew at an even faster pace. Substantial increases in Congressional appropriations for the NCI took place around 1947 and again in 1957, after the launch of the CCP and the creation of the CCNSC. While the growing

¹⁶ The role of philanthropic organizations in support of medical research deserves further comment, in light of the prominent role played by the American Cancer Society in the field of cancer research. It is noteworthy that while these organizations accounted for only 0.5 percent of the funding for general R&D in 1952, their share of medical research funding was as high as 27 percent in 1941 and declined over the following decade largely as the result of the growing commitment of R&D funds by government and other non-profit organizations, such as colleges and universities. It should also be noted that the attribution of research funding to philanthropic organizations and non-profit organizations concealed the possible role played by corporations as founders of and donors to such entities (Ladimer 1954).

commitment of public financial resources was undoubtedly a major development, the effective deployment of these resources faced considerable challenges.



Source: National Institutes of Health, Appropriations History by Institute/Center, https://officeofbudget.od.nih.gov/approp_hist.html.

Figure 1

Congressional Appropriations for NCI, 1938-1960 (thousands of current dollars)

The embryonic condition of the innovation system was most of all a reflection of the poor understanding of the etiology of most forms of cancer. Efforts at identifying substances with antitumor properties were based on an empirical approach rather than guided by specific knowledge of biological targets.¹⁷ As a result, the odds of success were low and the prospective costs of setting up an independent program for pre-clinical and clinical tests of anticancer drugs were high enough to deter individual pharmaceutical firms from escalating their involvement. Incentives for large privately-funded research programs were weakened further by the opportunity pharmaceutical firms had to collaborate with screening programs like the SKI's without losing control rights over proprietary compounds, and without shouldering the costs of carrying out pre-clinical or clinical investigations.

An important hurdle on the path to greater R&D efficiency was represented by the costs and uncertainty surrounding the use of murine models of tumor systems for pre-clinical testing.¹⁸ When the two systematic screening programs at the NCI and SKI got underway, each standardized much of their pre-clinical testing work on two of the available models of transplanted tumors, S37 and S180, respectively (Zubrod et al. 1966, 352). However, substantial concerns about the validity of these animal screens persisted. In light of the variety of forms of cancer, the effectiveness of each model as a screen for therapeutic effectiveness was poorly understood. The main problem was that there were only limited data about the

¹⁷ This type of search was not altogether blind, as conjectures about the causative mechanisms of tumors could be formulated, and search efforts directed to the exploration of analogs of substances whose anticancer properties had been observed empirically. The work of Hitchings and Elion was possibly an exception to this pattern, insofar as their search for effective drugs was an early instance of rational drug design (John E. Lesch 2008).

¹⁸ By the 1930s several murine models had been developed, including spontaneous and transplantable tumor systems. Much of this development work had taken place since the 1910s at the Roswell Park Memorial Institute in Buffalo, New York, and at the Roscoe Jackson Memorial Laboratories in Bar Harbor, Maine.

effectiveness of candidate antitumor substances in human cancer to guide the process of selection of effective animal screens (*ibid.*, 353). Further challenges were associated with the production of tumor-bearing mice. In a 1964 review of antitumor agents, Thomas A. Connors and Francis J.C. Roe (1964) described then-current practices in testing cancer chemotherapeutic substances as “an unstable and somewhat unhappy compromise between the desirable and the practicable” (Connors and Roe 1964, 827), lamenting in particular the need to rely on transplantable animal tumors (as opposed to spontaneous or induced tumors) which were “several steps removed from the real problem of finding drugs effective against spontaneous cancer in man” (*ibid.*, 828).

As noted above, constraints on the capacity to carry out clinical studies about the therapeutic value of substances that demonstrated antitumor properties in one or more murine models were a significant bottleneck for the development of critical knowledge. The unproven effectiveness of the chemotherapeutic approach to the treatment of cancer made recruiting subjects for clinical testing programs difficult. The frequently-observed toxicity associated with the administration of candidate substances led to the perception that clinical tests were an unnecessary and possibly immoral burden to place on suffering cancer patients, and on their families.

Moreover, scaling up a program of clinical tests required addressing substantial organizational challenges. Achieving sample sizes that could support sufficiently accurate inferences about the candidate drugs’ therapeutic value required extending the geographic scope of the search for candidate subjects, and thus the managerial complexity of the undertaking.¹⁹ This was especially important at a time when protocols for the clinical testing of drug candidates had hardly been developed. Variations in the conditions of the testing environment worked against the ability to learn from the tests, a fact of enormous significance in light of the many dimensions over which the administration of a cancer chemotherapeutic program could be differentiated. At a minimum, differences in the dosage and scheduling according to which drugs would be administered to the patient, effects from the interactions with other medicines, treatments, and other environmental factors, and the poorly-understood heterogeneity of patients’ response to all of the above, characterized a testing environment of extraordinary complexity whose management and standardization represented another costly challenge confronting any organization wishing to undertake large-scale clinical tests of anticancer drug candidates.²⁰

The Cancer Chemotherapy Program and CCNSC as Catalysts for Innovation System Development

The launch of a national cancer chemotherapy program and the creation of the CCNSC in 1955 were the culmination of a continuous increase in the commitment of public resources to fighting the scourge of cancer-related deaths. But they also marked a qualitative change in the modality of the government intervention with respect to the emergent innovation system for cancer chemotherapy. Influenced by the vision laid out by Bush (1945), the role of the US federal government in the national research enterprise included sponsoring both mission-oriented R&D work—often performed by industry actors—and basic scientific research performed by either governmental or non-profit organizations. The organization of the CCP

¹⁹ As noted above, the SKI’s screening program benefited from its partnership with the Memorial Hospital where clinical tests could be carried out under close supervision. A similar arrangement was in place in the UK, where the Chester Beatty Institute collaborated with the Royal Cancer Hospital in London.

²⁰ Peter Keating and Alberto Cambrosio (2012) provide an illuminating discussion of the challenges involved in establishing adequate protocols for clinical trials.

and of the CCNSC did not fit neatly into either of these two paradigms, representing rather a combination of both.

Although the search for adequate curative or palliative chemotherapies for the many forms of cancer was the mission underwritten by the US Congress, this mission could not be pursued effectively on the basis of extant R&D capabilities. Although cancer-related research had been funded for nearly a decade by the NCI—and support for basic research on cancer remained strong—the CCP was not meant to simply promote additional basic research efforts. Already in 1954, the Senate Appropriations Committee supported the organization of a directed program focusing on leukemia similar to those carried out during World War Two for malaria and antibiotics. While expressing continuing faith in and appreciation for the value of fundamental research carried out by grantees of the NCI, the Committee expressed this wish and appropriated an additional \$1 million for more work at the clinical level, noting that “the serial examination of clinical agents in the clinic has certain developmental aspects which could suitably be engineered” (Zubrod et al. 1966, 354).

Although the research community resisted the idea of a directed program, a voluntary effort at coordinating the clinical research work done by different grantee institutions got underway. This was sufficient to induce the Senate Appropriations Committee to propose additional funding (\$3 million) relative to the 1955 budget estimates for the NCI, so that these cooperative activities could grow further (ibid., 354-355). The belief that progress toward identifying a cure for cancer could be made or achieved more quickly on the basis of a more empirical approach to drug development was central to the launch of a cooperative program on chemotherapy of cancer in September 1954. This was modeled around the experience of the SKI program, which was seen as an exemplar of the coordination of the competences and resources of the multiple organizations and actors needed in the development of chemotherapeutic treatments for cancer.

The announcement of the CCP emphasized its service mission. Participants in the Program would benefit from access to the knowledge and information generated by the Program’s activities. At the behest of the Chemotherapy Committee of the National Advisory Cancer Council, the scientific community identified the following priorities for the Program (ibid., 355-356):

- (1) establish cooperative programs between chemists and biologists for drug screening;
- (2) secure adequate supplies of compounds of interest to permit their clinical evaluation;
- (3) expand pharmacological research on promising compounds;
- (4) expand clinical investigations to permit evaluation of promising drugs identified in pre-clinical tests.

The outline of the CCP was the result of consultations with industry representatives, other government and private agencies, leading to the creation of a Cancer Chemotherapy National Committee whose remit was to offer broad policy guidance for a national program sponsored by the NCI, the Veterans Administration, the Food and Drug Administration, the Atomic Energy Commission, the American Cancer Society, and the Damon Runyon Fund (ibid., 356).

The objective of the CCP was described as to “organize a drug development activity, supported by *contracts* for procuring drugs, evaluating those drugs for anticancer activity in animals, performing necessary preclinical studies, and, with support by special grants, clinical evaluations of promising drugs” (ibid., 356, italics mine). These activities were to complement an expansion of research activities funded by grants under conventional mechanisms, which supported research that was designed and controlled by the grantees. The coordination of

these functions was delegated to a new organizational unit, the CCNSC, which controlled or dictated the characteristics of the goods or services to be rendered under the contracts.

The scope of the CCP and the functions of the CCNSC align with several of the functions of a technology innovation system identified by Bergek et al. (2008), ranging from the development and diffusion of knowledge, and the mobilization of resources, to promoting a broad participation by actors from industry and the non-profit sector in the search for effective chemotherapies. Because of its coordinating role relating to activities performed by a multitude of private- and public-sector entities, the CCNSC operated as a public-sector drug development organization. Its activities contributed to the development of not only specific anticancer drugs, but also of an institutional and technological infrastructure that ultimately became the backbone of the cancer chemotherapy innovation system.

It should be noted that the CCNSC's activities built upon the template of the large-scale screening program that inspired the foundation and operations of the SKI. But leveraging the financial resources committed by the US government, the CCNSC was able to scale up the approach, coordinate a broader research effort, and seed the growth of centers of pre-clinical and clinical research in different locations in the US.²¹

The development of the CCP by the CCNSC was overseen by a handful of scientific panels whose membership included leading scientists in the relevant fields. These panels played a crucial role in designing the structure of the cooperative program, making critical recommendations about the allocation of funds, and mobilizing individual scientists and external organizations whose participation in the cooperative program was considered essential. Our selective review of the activities of the CCNSC will begin with a review of the interactions with the chemical and pharmaceutical firms whose participation in the CCP was considered a key to the success of the screening program. Later sections will briefly comment on the activities overseen by the Screening Panel and the Clinical Panel.

Industry's Participation in the Program

Securing the participation of business firms in the chemical and pharmaceutical sectors was seen early on as a requisite for the successful implementation of the CCP. To this end, the Chemotherapy Committee of the CCNSC relied upon the policy advice of an Industry Subcommittee organized in 1955, whose membership consisted of research personnel from pharmaceutical and chemical companies (Zubrod et al. 1966, 359). The Subcommittee facilitated communication between the CCP leadership and industry.

Pharmaceutical and chemical firms were expected to participate in the CCP in a variety of ways. In particular, they were expected to:

- (a) submit compounds to the CCNSC for them to be screened for antitumor properties;
- (b) supply chemicals, equipment, experimental animals, and testing services;
- (c) contract in the synthesis of new chemicals or the development of laboratory methods;
- (d) engage in independent research activities related to the Program under contract with the National Institutes of Health (NIH).

Meeting these expectations required addressing industry partners' concerns relating to the handling of confidential information and IPR under the legal instruments governing the

²¹ For perspective, Alfred Sloan indicated that the SKI operated around 1952 with a budget of about \$2.5 million (US House of Representatives, Select Committee to Investigate Tax Exempt Foundations and Similar Organizations 1953, 455). The US Congress appropriated nearly \$20 million for the NCI in that year.

interactions between private firms and governmental entities or their contractors. While business firms were initially reluctant to cooperate with the CCP, adaptations of contract policies and of department rules regarding the disposition of intellectual property were later adopted in such a way as to ensure broad participation (*ibid.*, 361).

The use of contracts was a novel administrative mechanism for the NIH—first authorized in fiscal year 1956, so that contract policies had to be developed on the fly. Whereas handling of contracts related to (b) above was a simple task, contracts for areas (a), (c), and (d) raised important questions about confidentiality of information on the results of screening tests, research, methods, and the like, and about the assignment of property rights over any inventions occurring in the context of contract performance.

As the submission of chemical substances for screening and testing was governed by the contract policy of the DHEW, pharmaceutical and chemical firms had to be concerned with the dilution of their proprietary interests in any compounds that showed antitumor activity. Under the Department's "standard" patent clause for research contracts, the Surgeon General held the right to determine the disposition of inventions arising from the performance of the contract in such a way as to promote the public interest. Because of the uncertainty about how this policy would apply to the submission of compounds to the CCNSC for screening, industry participation was modest indeed during the first year of operation—only one firm (Upjohn) submitted any compounds to the CCP.

The impasse was resolved when the DHEW, amended the patent policy applicable to research contracts related to the CCP. Specific provisions for the contracts with suppliers of chemical compounds for screening and testing established that all rights remain in the company, and that the company may be given a right to confidentiality over the results of the screening tests for a period not to exceed twelve months. The policy also stipulated that when the testing and screening activity was contracted out by CCNSC to an outside laboratory, the contract with the latter would contain provisions safeguarding the rights of the compounds' supplier.

Following these amendments to the patent policy, industry firms accounted for about half of the compounds that were submitted to the CCNSC. By the second year of activity, the CCNSC was receiving on average ten thousand synthetic compounds per year, requiring nearly 50,000 tests per year (*ibid.*, 361). The flow of submissions from industry firms increased further once the potential of broad-spectrum antibiotics in the chemotherapy of cancer was demonstrated by Sidney Farber's experimental work in 1955 (Farber 1966). Since the development of antibiotics had been an important area of specialization for pharmaceutical firms during the early 1950s, these firms could draw from a substantial library of antibiotic culture broths whose antitumor properties could be assessed in the context of the CCP. The submissions of antibiotic cultures from major pharmaceutical firms, including Pfizer, Merck, Abbott, Upjohn, Bristol, Squibb, Parke-Davis, and others, rose considerably during the following years, increasing substantially the screening capacity needs of the CCNSC. While the CCNSC responded to this situation by contracting for screening services with additional research institutions, it became necessary for at least a few pharmaceutical firms to establish in-house screening laboratories (Zubrod et al. 1966, 361-362).

IPR issues were also relevant to the negotiations of research contracts between the CCP and industrial firms. Although the initial approach was to extend to research contracts the same policy that the NIH applied to research grants more generally, it became apparent that the generic patent policy was going to be an obstacle from the viewpoint of the industrial firms' participation in the CCP. Consequently, a few alternative methods for addressing IPR issues were designed. The research contracts signed by CCNSC could contain the "standard patent clauses" reserving to the Surgeon General the right to determine the disposition of inventions under the contract, or an "alternative clause" reserving to the contractor the rights to any invention conceived or reduced to practice in the course of performance, subject to a

number of limitations.²² First, the contractor agreed to report promptly any invention to the Service through an invention report. Second, the contract reserved to the Government the right to make a disclosure of the invention after allowing the contractor an opportunity to protect its own proprietary interests. Third, the contract reserved a non-exclusive royalty-free license to use the invention for government purposes. Fourth, the contract specified a process through which the Government could exercise “march-in” rights in order to meet health needs not addressed by the contractor.²³ Fifth, the contract reserved to the Service the option to assert proprietary interest in the domestic and foreign rights to the invention following a contractor’s determination not to patent. Finally, a non-mandatory provision was that the contract might be renegotiated in case the contractor decided to pursue new leads identified in the course of performance at its own expense.

These contractual provisions were the result of complex and prolonged negotiations. The first date of availability of the “alternative clause” was September 9, 1957, when such clause left the exercise of march-in rights by the government to the discretion of the Surgeon General. This policy was later reviewed by the DHEW’s Patent Policy Board, which had been notified by the Surgeon General about the Service’s inability to conclude any research contract on the basis of the September 1957 policy. The Board received written comments from the American Drug Manufacturers Association (ADMA) and heard industry representatives (US Senate Committee on the Judiciary 1961, 22).²⁴ The industry’s main concern was that the Surgeon General might give in to the pressure of public opinion in support of the exercise of march-in rights and the consequent non-exclusive licensing of inventions conceived during the performance of the research contract. The result of this policy review was the drafting of a new “alternative clause” —announced on August 5, 1958—whereby the exercise of march-in rights by the Surgeon General was subject to formal proceedings.

These exceptions to the standard patent policy were the result of concerns that went well beyond the specific focus of the CCP, and the desire by industry participants to protect and leverage their existing patent portfolios.²⁵ In particular, it was understood—and feared, in the case of the industry—that research activities carried out in the context of the research program formally directed at cancer could identify the potential usefulness of compounds for other kinds of diseases. The CCP was also a first foray by the government into research activities that were much closer to industrial firms’ interests in the development and production of novel drugs. The ADMA had in fact expressed strong opposition in 1958 to the prospect that the model of government participation in R&D for cancer chemotherapy might be replicated for other areas of pharmaceutical research. In the words of Karl Bambach, executive vice president of ADMA: “The cancer chemotherapy program definitely should not

²² The expression “reduced to practice” is used in intellectual property law to distinguish the mere conception of an invention (usually held in the mind of the inventor) from its actual implementation or its description in terms that would allow anyone with ordinary skill in the relevant art to implement it.

²³ “March-in” rights are government rights to grant licenses on the contractor’s patents to third parties, the exercise of which would amount to taking over the management of the contractor’s patents.

²⁴ These representatives included the president of Merck & Co., the chairman of the board of Abbott Laboratories and ADMA president, and the president of Schering Co., who was also president of the American Pharmaceutical Association.

²⁵ From the viewpoint of the Public Health Service patent policy, the exceptions to the policy governing research contracts created for the CCP did not appear to have substantial diffusion outside the Program. In testimony before the US Senate Subcommittee on Monopoly of the Select Committee on Small Business Committee, Parke M. Banta, legal counsel of the DHEW, noted that only 12 of the 227 research contracts signed by the Public Health Service during 1958-59 related to the CCP and left patent rights to contractors (US Senate Select Committee on Small Business 1959, 356).

be used as a pattern to be applied to fields where good drugs already exist, and where intensive company research is going on".²⁶

These concerns notwithstanding, the introduction of the 1957 patent clause promoted widespread industry participation in the CCP. By 1965 pharmaceutical and chemical firms featured prominently among the contractors that collaborated with the CCNSC in several areas—ranging from drug procurement, natural products development, drug evaluation, as well as R&D related to new screening methods, and studies of mechanisms of action. The Program was instrumental in promoting the mobilization and integration of these firms in the emerging innovation system for cancer chemotherapy.

Screening Activities

Scaling up the screening of substances and compounds was a primary goal of the CCP. While screening activities had been fairly successful at identifying promising candidates for drug development in other areas of pharmaceutical development, much work had to be done before a large effort could be undertaken in the area of cancer chemotherapy. Throughout its first decade of operation, the CCNSC engaged in the development and refinement of effective screening protocols, and contracted with a growing number of counterparts from the private and non-profit sectors for research on and the production of laboratory animals and cellular screens.

Within a short time after it was convened, the Screening Panel surveyed existing screening procedures and recommended that three tumor systems be used in all pre-clinical testing, namely S180, Ca755, and L1210. An earlier study commissioned by the NCI had shown that together these tumor systems demonstrated antitumor activity for all substances known to be useful in humans. The Panel established protocols for how these tumors were to be used in service contract laboratories of the Program and arranged for the scaling up of the breeding facilities of the Jackson Memorial Laboratories in Maine so that the production of 100,000 inbred mice a year could be attained within a short time (Zubrod et al. 1966, 358).²⁷ This production level was thought to be sufficient to meet the demand associated with the 12,000 tests per year that the Panel expected would be carried out for 3,000 to 4,000 compounds. These estimates proved to be too low; government and university sources submitted around 5,000 compounds to the CCNSC for testing between November 1955 and June 1956. This larger-than-expected flow reflected the latent demand for access to screening facilities expressed by chemists whose research had been supported by NCI grants (*ibid.*, 360-361).

Meeting this demand was a challenge. Although the Screening Panel had moved quickly with selecting the tumor screens, the organization of the screening laboratories took longer. Universities were not interested in carrying out large-scale screening tests, so that the CCNSC turned to nonacademic organizations as the prospective contract partners. With the exception of the Southern Research Institute which had cooperated with the SKI in earlier times, there were no research organizations that could offer the screening services that the CCNSC needed. In the end, five screening services contracts were signed with as many research organizations (Southern Research Institute, Stanford Research Institute, Wisconsin Alumni

²⁶ The quote is from a presentation on "The Washington Scene and the Drug Industry" delivered by Karl Bambach at the Rutgers Pharmaceutical Conference in New Brunswick, New Jersey, on May 14, 1958. The presentation is reproduced in US Senate Subcommittee of the Committee on Appropriations 1958, 1679-1684.

²⁷ The Panel also recommended the development of a similar capability on the West Coast of the US.

Research Foundation, Microbiological Associates, and Hazleton Laboratories) for a sum of nearly \$450,000 (*ibid.*, 361).²⁸

Within six months, these screening centers received 4,337 compounds and submitted 5,543 test reports. The number of tests fell short of projections, a result of the bottlenecks encountered in the production of inbred mice for the tumor systems Ca755 and L1210. Almost all of the tests carried out at the screening laboratories were based on the S180 tumor system which did not require inbred mice. Production capacity for S180 was nearly 2 million tests per year, a quantity that could easily meet the needs of the screening program. In contrast, the existing inbred mice production capacity was insufficient both in terms of quantities (about a quarter million units) and in terms of genetic, disease, and quality control procedures.

The CCNSC played a significant role in addressing these weaknesses, leading to the establishment and modernization of facilities for genetic research and production of laboratory animals at universities and commercial organizations. Together with the development of production standards and a corresponding accreditation program, the activities of the CCNSC in this area promoted a broad-based diffusion of capabilities that supported research not only in the field of cancer chemotherapy but also across the spectrum of pharmaceutical R&D (*ibid.* 1966, 363-365).

The Screening Panel devoted much attention to the study of efficient experimental designs. A key role in this respect was played by Peter Armitage, a scientist from the London School of Hygiene, who visited the CCNSC in 1957. The experimental sequential test design developed by Armitage and other scientists at the NCI made it possible to complete testing of inactive compounds with an average of 4.7 tests. Further cost savings were sought in the reduction of the number of mice needed for every test group. As a result of this multi-faceted effort, the CCNSC's screening laboratories experienced a reduction of the average cost of a screening test from \$85 to \$25-\$30 (*ibid.*, 361-363).

The Clinical Panel

Of course, the ultimate objective of the screening activities was to identify a number of promising leads that could undergo clinical tests for antitumor activity in humans.²⁹ This required that preparations be made for carrying out clinical trials of either compounds whose anticancer properties had already been established or compounds whose potential therapeutic value had been established on the basis of screening activities. The experience of SKI's screening program suggested that about one substance would be a candidate for clinical testing for every 1,000 compounds screened in the laboratory. This was the basis for the initial estimates guiding the Clinical Panel about the need for clinical testing capabilities.

A major challenge confronted by the Clinical Panel was the organization of large-scale inter-institutional collaborative clinical trials. Little was known about the kinds of problems that would arise, and it was expected that much of the learning would occur as a result of direct experience. The condition of relative ignorance made it all the more important that knowledge resulting from the organization of clinical testing activities be shared widely. During his 1957 congressional testimony, Dr. Sidney Farber—then chairman of the Committee on Chemotherapy of the National Advisory Cancer Council—emphasized the significance of the new methods adopted by the CCNSC staff for communicating research results as rapidly and

²⁸ These research organizations were selected partly because of their proximity to cancer research institutes with which they were expected to collaborate.

²⁹ Keating and Cambrosio (2002) provide an excellent account of the evolving relationship between the screening activities of the CCP and the clinical testing of drug candidates, arguing that by the early 1960s clinical research had developed into an autonomous component of the overall research enterprise, capable of generating research leads and methods that reduced its dependence on inputs from *upstream* screening activities.

widely as possible (US House of Representatives, Committee on Appropriations, 1956, 57-58).

The first cooperative study groups had been formed in 1955, two of them concerned with the treatment of leukemias (Acute Leukemia Group A and Acute Leukemia Group B) and one concerned with solid tumors (Eastern Solid Tumor Group). The activities of these groups were at first directed toward carrying out tests of drugs that were already in clinical use, in order to analyze more systematically their antitumor properties and to accumulate experience in the design and management of inter-institutional collaborative trials.³⁰

The number of cooperative groups grew steadily as clinicians from medical centers and universities across the country became increasingly eager to participate in the clinical tests and later research organized by the CCNSC. Although these groups came under intense criticism at various points during the CCP's first decade, the CCNSC proved to be receptive to constructive criticism, reasonably quick at adapting protocols and selection criteria for the allocation of grant and contract funds, and capable of accommodating the interests of newly-forming collaborations among clinicians focused on specific types of cancer.³¹

Among the working committees established by the Clinical Panel, the Experimental Design Committee and the End Results Committee made highly significant contributions by developing respectively the statistical techniques necessary to improve the efficiency of testing protocols, and the data-collection infrastructure (in the US and abroad) necessary to record the natural history of cancer.

By 1965, the cooperative studies program had grown to include 1,000 clinical investigators operating at 300 institutions (Zubrod et al. 1966, 399), and had supported clinical trials for more than 150 drugs, including much of the clinical work that led to expedited approval of seven antitumor drugs. From the viewpoint of this article, an equally interesting outcome of the CCP was the development of the national clinical research infrastructure that could carry out assessments of novel drugs according to well-defined protocols and based on appropriate statistical techniques.

Conclusion

Adopting the analytical frame of technology innovation systems, this article has revisited the literature on the origin and activities of the CCNSC and examined the latter's contributions to the development of actors and relations within the innovation system focused on cancer chemotherapy. While these contributions could be thought of as secondary effects of the US government's CCP, they were arguably the most significant outcome of a program whose direct and indirect impacts on the development of novel cancer treatments took shape only decades later.

The CCP was an innovative undertaking. While it encompassed conventional forms of public support to research carried out by private and non-profit organizations, the Program's goals went much further and aimed at the development of novel cancer drugs. Although earlier screening programs had led to the identification of a handful of drugs, the innovation system was underdeveloped. Pharmaceutical firms' research was limited in light of the uncertainty surrounding the prospects of cancer chemotherapy, and so was the capacity for carrying out research in the various phases of the drug development process. Shortly after the launch of

³⁰ Thus, the Panel arranged for a comparative study of thioTEPA and nitrogen mustard against cancer of the lung, breast, Hodgkin's disease, and melanoma. This was carried out by the Eastern Solid Tumor Group, and launched successfully on March 1, 1956, enrolling 50 patients within three months (Zubrod et al. 1966, 358).

³¹ Alfred Gellhorn, director of the Institute of Cancer Research at Columbia University, criticized repeatedly the allocation of excessive resources to the empiricist approach to the search for cancer drugs (Gellhorn 1959).

the CCP and the establishment of the CCNSC, Cornelius Rhoads expressed the view that progress in cancer research called for providing “support on a substantial scale for a substantial period: time enough to get this job done and not just dabble at it” (US House of Representatives, Committee on Appropriations 1956, 48).

In the long run, the CCP was credited with contributing to the development of most anticancer chemotherapeutic substances available as late as the mid-1980s (DeVita and Chu 2008) and demonstrating the therapeutic value of combination chemotherapy, a treatment regime based on the combination of multiple drugs. While these are important outcomes, the emphasis in this article has been on the contributions of the CCP and CCNSC to the development of the innovation system focused on cancer chemotherapy. By reference to the taxonomy of system functions proposed by Bergek et al. (2008), these contributions were most notable in the areas of resource mobilization, development and diffusion of knowledge, influencing the direction of search, and legitimation of the chemotherapeutic approach. A central objective of the CCP was to promote the participation of external actors in the scaling-up of cancer research. To this end, the financial resources of the CCP were deployed to promote the mobilization of existing resources and the development of new ones. Especially noteworthy was the stimulus that the Program provided to the development of mice-breeding facilities in support of research, the establishment of novel screening laboratories and the scaling-up of existing ones, as well as the involvement of large numbers of medical centers in clinical testing and research. The engagement of chemical and pharmaceutical firms was a crucial goal of the CCP insofar as they were expected to be the most important source of compounds and substances for evaluation in the screening program. Attaining this goal required the adaptation of NIH policies related to the handling of IPR issues.

Debates over the federal government patent policy around that time were mostly concerned with the difficulties encountered by NIH grantees at securing the cooperation of pharmaceutical firms for screening novel compounds. The argument that pharmaceutical firms would not incur these screening costs unless they could secure exclusive rights to the development of active substances was very important in promoting the changes in federal policy that culminated in the Bayh-Dole Act.³² In the area of cancer chemotherapy research, the roles of pharmaceutical firms and the public sector were reversed, so to speak. When the CCNSC offered to screen existing compounds for antitumor properties at public expense, the pharmaceutical industry refused to participate in the CCP until the NIH agreed to amend its patent policy so as to protect the supplier’s proprietary interests in the compounds. This resolution of the conflict between the pharmaceutical firms and the NIH cemented the control that the pharmaceutical industry had on the commercialization of pharmaceutical innovations that were in varying degrees the result of publicly-funded research. As noted above, the industry did not see favorably the kind of government-funded foray into drug development represented by the work of the CCNSC.

The CCP made important contributions to various aspects of knowledge related to the development of pharmaceuticals. These ranged from the continuing development of statistical methods for designing tests and evaluating their results, protocols for clinical trials, methods for inter-institutional coordination, and a substantial body of information and knowledge about any forms of cancer. Knowledge emanating from the activities sponsored by contracts and grants was disseminated widely through scientific journals and through dedicated publications such as the Cancer Chemotherapy Reports.

³² A primary goal of the Bayh-Dole Act of 1980 was to promote more extensive commercial application of the results of federally-funded research. In particular, the Act made it a general policy of the federal government to allow universities and university scientists to retain intellectual property rights on the results of research carried out with federal funds and endorsed the granting of exclusive licenses on such rights to industrial firms.

Furthermore, the CCP contributed to the growth of technological and research capabilities of both pharmaceutical firms and of firms and organizations providing tools and services related to all phases of pharmaceutical R&D. Arguably, the CCP was responsible for carrying out an important share of the infrastructural investments that ultimately supported the development of an innovation system for cancer chemotherapy whose activities did not benefit from financial support by private firms until two decades later. To be sure, expectations that the Program would lead to short-term progress in the treatment of various forms of cancer were disappointed, something that fueled debates concerning the most effective use of the public resources appropriated for cancer-related research.³³ But surely public investments of the kind that supported the CCP would have been unnecessary if successful results in the development of pharmaceutical treatments for various forms of cancer could have been expected in a short time!

We know in hindsight that finding effective chemotherapeutic treatments for cancer was a substantial challenge, calling for unprecedented financial efforts and extraordinary advances in scientific knowledge. That the US government took on this challenge at a time when private investment in the area was absent suggests that the early history of the CCP illustrates the investment activities of what Mariana Mazzucato has called an *entrepreneurial state* (2013, 5). In light of the pervasive uncertainty surrounding these kinds of investments, this article has proposed that the economic and social benefits of the CCP and of the activities of the CCNSC be evaluated from the viewpoint of the institutional developments that they promoted and the impulse they gave to the creation of an innovation system focused on cancer chemotherapy. While the CCNSC was billed as a decentralized drug development organization, these developments—rather than the count of drugs developed—were arguably its most important legacy.

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³³ Some critics of the public drug development program suggested that greater funding of basic research related to cancer would have been a more productive use of the public resources (Gellhorn 1959, 6). The notion that progress in the treatment of cancer could only happen after a more complete understanding of the disease was obviously antithetical to the overall philosophy of the screening programs. As noted by Isidor S. Ravdin, chairman of the Clinical Studies Panel in 1959: "The history of other significant advances in therapy would suggest to me that perhaps those who believe that all progress will be made through basic science alone are not fully conversant with previous contributions to medicine" (Ravdin 1959, 13).

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