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Microbial Transformations: The Japanese Domestication of Penicillin Production, 1946–1951

ABSTRACT

The domestication of penicillin production in Japan was a priority for the Allied occupation government (1945–1952) immediately after World War II, since manufacturing the drug using raw materials available locally would lower the cost of the occupation. In place of employing the analytical concept of technology transfer, this article explores processes of domestication (*kokusanka*) using the records of the Japan Penicillin Research Association (Nihon penishirin gakujutsu kyōgikai), an interdisciplinary academic association set up to mediate between government policy and industrial manufacturers, and which directed research in the critical early years of penicillin production. I argue that an examination of the occupation period is especially revealing of the contribution of indigenous knowledge from the World War II and prewar periods to the development of microbiology during Japan's "economic miracle" (1950s to early 1970s), and I highlight the intellectual dimensions that were specific to Japanese science by comparison with other national cases of penicillin domestication. Beyond the transfer of submerged culture fermentation technology for antibiotic mass production, a distinctive engagement with agricultural chemistry's longstanding perception of microbes—as alchemists of the environment, with the ability to transform resource scarcity into productive abundance—organized the

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The following abbreviations are used: GHQ, General Headquarters; ISS, Istituto Superiore di Sanità (National Institute of Health, Italy); JARA, Nihon kōseibusshitsu gakujutsu kyōgikai (Japan Antibiotics Research Association); JPMA, Shadan hōjin Nihon penishirin kyōkai (Japan Penicillin Manufacturing Association); JPRA, Nihon penishirin gakujutsu kyōgikai (Japan Penicillin Research Association); MITI, Tsūshō sangyō shō (Ministry of International Trade and Industry, Japan); NIH, Kokuritsu yobō eisei kenkyūjo (National Institute of Health, Japan); NPGKK, Nihon penishirin gakujutsu kyōgikai kiji (Records of the Japan Penicillin Research Association); SCAP, Supreme Commander for the Allied Powers.

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knowledge by which penicillin scientists made the domestic environment work, and deeply shaped antibiotic research in the subsequent decades in Japan.

KEY WORDS: microbiology, penicillin, antibiotics, chemical industry, technology domestication, interdisciplinary research, planning, Japan

INTRODUCTION

On August 15, 1946, the presidents of thirty-nine Japanese companies gathered with Ministry of Health and Welfare officials at the opening meeting of the Japan Penicillin Manufacturing Association (Shadan hōjin Nihon penishirin kyōkai, JPMA) at the Seiyōken Hall in Ueno, Tokyo. The attendees included the presidents of the largest permitted manufacturers at the time—pharmaceutical companies Banyū Seiyaku, Morinaga Yakuhin, and Wakamoto Seiyaku—as well as other pharmaceutical and chemical manufacturers such as Dainippon Seiyaku, Yaesu Kagaku, and Wakōdō, and the dairy company Meiji Nyūgyō. Iwadare Tōru, then president of Banyū Seiyaku, later recollected that "it seems strange to think of it now, but at the time both the government and firms were not very enthusiastic about developing penicillin."[1] In fact, at the time almost no factories in Tokyo were in operation at all, except small workshops turning out goods for the black market. It was the first anniversary of the surrender that had ended World War II.

In the difficult conditions of sheer material scarcity that marked the years immediately after the war, officials, academic scientists, and industry leaders met to begin discussions on the domestication of penicillin mass manufacture. To address the problem of raising the quantity and quality of domestic production, the Ministry of Health and Welfare had proposed two new associations on behalf of the Allied occupation government: one a corporate body to encourage exchange between penicillin manufacturing firms, the Japan Penicillin Manufacturing Association as described above; and a second, separate, *academic* body to coordinate laboratory research on production problems, which would form the Japan Penicillin Research Association (Nihon penishirin gakujutsu kyōgikai, JPRA). It is the work of the second body, the academic association known as the JPRA, that is the focus of this article.

1. Nihon penishirin kyōkai, ed., *Penishirin no ayumi* [History of penicillin] (Tokyo: Nihon penishirin kyōkai, 1961), 3. Unless otherwise credited, all translations are done by the author.

Penicillin's mass production was originally a triumphant legacy of the World War II biomedical research complex in the United States. Penicillin was not difficult to produce in small quantities at the laboratory bench, but the challenge was in making cheap, large-scale manufacture possible so that penicillin could be widely available for clinical use. During wartime, the British team of scientists who had attained small amounts of penicillin from the *Penicillium* mold at the laboratory bench took penicillin to the United States to seek manufacturers willing to scale up production. At the U.S. Department of Agriculture's Northern Regional Research Laboratory in Peoria, Illinois, scientists made commercial-scale fermentation possible using a submerged culture (also called deep fermentation) tank, where strains were grown throughout the culture medium, rather than only on the surface as had been previously done at the bench. Unlike surface culture, submerged culture for aerobic processes such as penicillin fermentation was complex to engineer: it required a supply of air into the liquid culture medium in the tank and stirring to disperse the air bubbles to the strains, as well as temperature control and sterile conditions. A major innovation that allowed inexpensive manufacture was the use of corn steep liquor as a culture medium, which was as effective as it was cheap and abundant in the region.[2]

Because of the specific narrative of the American achievement in mass production, historians who have considered Japanese penicillin as a case of technology transfer within the pharmaceutical industry often identify submerged culture fermentation (deep fermentation) to be the heart of expertise in penicillin and antibiotic production technology.[3] Yet, although the transfer of submerged culture technology from the United States was indeed new and pivotal to Japanese fermentation expertise, a story of the technology transfer of submerged culture alone does not sufficiently account either for *how* Japanese scientists and manufacturers so rapidly assimilated antibiotic technology in domestic material conditions, nor for *why* antibiotic science in Japan subsequently developed as it did. Penicillin production during the Allied occupation

2. Peter Neushul, "Science, Government, and the Mass Production of Penicillin," *Journal of the History of Medicine and Allied Sciences* 48 (1993): 371–95.

3. Maki Umemura, *The Japanese Pharmaceutical Industry: Its Evolution and Current Challenges* (Abingdon, Oxon: Routledge, 2011), ch. 3; Julia Yongue, "The Introduction of American Mass Production Technology to Japan during the Occupation: The Case of Penicillin," in *Organizing Global Technology Flows: Institutions, Actors, and Processes*, eds. Pierre-Yves Donzé and Shigehiro Nishimura (New York: Routledge, 2014), 213–29; Daniele Cozzoli, "Penicillin and the Reconstruction of Japan," *Medicina nei secoli arte e scienza* 26, no. 2 (2014): 469–84.

period built upon as well as transformed Japanese microbial science and industry. The country successfully mass-produced penicillin domestically and achieved self-sufficiency as early as 1948, the third country to do so after the United States and Britain. In the subsequent decades, Japan emerged as a leading center of antibiotic research and innovation—including critical work in stabilizing fermentation methods, elucidating the genetic mechanisms of antibiotic resistance in bacteria, and developing new mold-based drugs including statins and avermectin. (The anti-cholesterol drugs known as statins are among the best-selling drugs in pharmaceutical history, and work on the antibiotic avermectin earned Ōmura Satoshi of the Kitasato Institute the 2015 Nobel Prize in Physiology or Medicine.)[4]

Technology transfer, especially from the United States, is a persistent theme in accounts of Japan's postwar high-speed economic growth from the 1950s to the early 1970s. In particular, accounts often emphasize the guiding hand of the Ministry of International Trade and Industry (MITI) in promoting technology transfer for strategic sectors and industry winners, especially in the electronics and automobile industries. The story of penicillin production, which took place *before* Japan's economic miracle, casts a different light on the high-growth era.[5] An examination of early antibiotic science in the

4. By 2002, Japanese laboratories had developed over 117 useful antibiotics and other bioactive microbial metabolites; see Joichi Kumazawa and Morimasa Yagisawa, "The History of Antibiotics: The Japanese Story," *Journal of Infection and Chemotherapy* 8, no. 2 (2002): 125–33. On Japanese contributions to production methods and antibiotic resistance research, see, respectively, Robert Bud, *The Uses of Life: A History of Biotechnology* (Cambridge: Cambridge University Press, 1994), and Angela N. H. Creager, "Adaptation or Selection? Old Issues and New Stakes in the Postwar Debates over Bacterial Drug Resistance," *Studies in History and Philosophy of Biological and Biomedical Sciences* 38 (2007): 159–90.

5. It is easy to see any kind of mid-twentieth-century knowledge transfer from the United States to Japan as being part of a broader story of international development with American visions and ideals at its core, not least because the Japanese example has often been invoked in the context of modernization theory; for a concise summary of the literature on American models of international development in science and technology during the Cold War, see Audra J. Wolfe, *Competing with the Soviets: Science, Technology, and the State in Cold War America* (Baltimore: Johns Hopkins University Press, 2013), ch. 4. Yet, this would be a superficial reading of Japanese penicillin production in the early occupation years. The domestication of penicillin production was mostly achieved before the Cold War began to shape the occupation government's policies, and well before the height of influence of modernization theory. Moreover, it is well known that the occupation state—though centralized and authoritarian—was thin on the ground and relied on indirect rule through the existing bureaucracy; see John W. Dower, *Embracing Defeat: Japan in the Wake of World War II* (New York: W. W. Norton & Co., 1999), 212–13. The Ministry of Health and Welfare oversaw developments in the pharmaceutical industry.

occupation years reveals the indigenous contribution of both *institutions* and *expertise* to the postwar development of Japanese science and technology. In his classic study of MITI, Chalmers Johnson highlights the transwar origins of industrial policy itself, tracing MITI's continuity with wartime and prewar bureaucratic organizations.[6] More recently, historians of Japanese engineering as well as biomedicine have argued similarly that post–World War II achievements relied on experts' wartime and prewar experiences, rather than emphasizing post–World War II knowledge transfer.[7]

In place of technology transfer, this article focuses on the phenomenon of "domestication" (*kokusanka*) in order to explore the creativity that is necessary in import substitution. How did scientists try to make things work?[8] Experts in Japan faced a quite different set of material constraints immediately after World War II than they would in the following decades. Both Japanese and American perspectives from the period stress the starkness of material scarcity. The term "domestication" was the main term used by government officials, scientists, and manufacturers to describe the goals for penicillin production in Japan at the time. In that context, the term specifically referred to achieving the capacity to manufacture penicillin—in mass quantities and to an adequate quality—using raw materials available locally.

But the word "domestication" had another, broader meaning, which would have been equally resonant to Japanese technical experts in the period. Historian Daqing Yang describes how the connotations of "domestication" shifted from merely indigenous manufacturing in order to reduce imports of specialized equipment in the 1920s, to a movement that sought to promote the completely independent development of innovative technologies that would use raw materials from Japan's Asian empire in the 1930s and 1940s.[9] Thus, the word carried wartime associations with both autarky and imperialism; while

6. Chalmers Johnson, *MITI and the Japanese Miracle: The Growth of Industrial Policy, 1925–1975* (Stanford, CA: Stanford University Press, 1982).

7. Takashi Nishiyama, *Engineering War and Peace in Modern Japan, 1868–1964* (Baltimore: Johns Hopkins University Press, 2014); Akihisa Setoguchi, "Control of Insect Vectors in the Japanese Empire: Transformation of the Colonial/Metropolitan Environment, 1920–1945," *East Asian Science, Technology and Society* 1 (2007): 167–81; Iijima Wataru, *Mararia to teikoku: Shokuminchi igaku to Higashi Ajia no kōiki chitsujo* [Malaria and empire: Colonial medicine and the East Asian regional order] (Tokyo: Tōkyō daigaku shuppankai, 2005).

8. The conception of the problem of "making things work" comes from the Histories of Planning project led by Dagmar Schäfer at the Max Planck Institute for the History of Science.

9. Daqing Yang, *Technology of Empire: Telecommunications and Japanese Expansion in Asia, 1883–1945* (Cambridge, MA: Harvard University Press, 2011), ch. 4.

kokusanka is translated by Yang as "domestic production," it was also allied with the military-linked idea of self-sufficiency. Here "domestication" is chosen as the translation for *kokusanka* because the term conveys the attempt to achieve change (*ka*) along a continuum from technology transfer to import substitution, rather than positing a sharp distinction between the two in actors' categories. It is worth remembering, however, that the related notion of Japan as a resource-poor country was used to justify imperial expansion.[10]

Contrary to wartime rhetoric, Yang emphasizes that the shift in the meaning of "domestication" was motivated by a combination of "material, ideological, and personal" demands, and not solely by material need arising from geopolitical circumstances.[11] Material scarcity was most apparent only in the final years of the war and after the surrender.[12] Japanese fermentation scientists working immediately after World War II drew on similar experiences from the wartime period and applied them to the problem of penicillin domestication. For a variety of historical reasons, then, which were partly but not entirely material, fermentation scientists' knowledge and institutions were organized around the salience of resource scarcity in motivating experimentation: more specifically, they saw microbes as tools of abundance in the midst of resource scarcity.

The "microbial transformations" in the title of this article describes the perceived role of microbes as alchemists of the environment. I argue that such a perception of microbes organized the existent knowledge by which penicillin scientists made the environment (in a material as well as sociopolitical sense) work. Rather than tracing the historical roots of fermentation scientists' knowledge and institutions to make the case for epistemic continuity, this article instead explores the specific dimensions of Japanese fermentation expertise in the occupation era using two other methods. First, I examine processes of the domestication of penicillin production through the JPRA records, which have

10. Hiromi Mizuno, *Science for the Empire: Scientific Nationalism in Modern Japan* (Stanford, CA: Stanford University Press, 2009); Janis Mimura, *Planning for Empire: Reform Bureaucrats and the Japanese Wartime State* (Ithaca, NY: Cornell University Press, 2011).

11. Yang, *Technology of Empire* (ref. 9), 158.

12. The environmental conditions during wartime have been detailed by William Tsutsui, who suggests that the impact of 1940s material scarcity on postwar practices would make an interesting question for further research: "The profound, often crippling wartime shortages of natural resources—especially fossil fuels—had the effect of driving many Japanese—from housewives to corporate engineers to university scientists—to new extremes of desperation, frugality, and creativity"; William M. Tsutsui, "Landscapes in the Dark Valley: Toward an Environmental History of Wartime Japan," *Environmental History* 8 (2003): 303.

not hitherto been analyzed historically.[13] Second, I compare Japanese developments with a number of other national cases of penicillin domestication, drawing on a strong secondary literature on Europe in the wake of World War II. The comparisons are both institutional and conceptual; since skill is embodied in personnel, attention to institutions is required to fully understand the nature of knowledge.[14]

In this way, the article contributes to a growing literature on biological research in the chemical industry. Production-related questions for penicillin—for example, problems of screening (how does one select the microbial strains that can best perform the task of penicillin fermentation?), or contamination (how does one ensure that the stray presence of other microbial strains in the fermentation tank will not impede penicillin fermentation?)—point to a distinctive history of *biological materials* within chemical manufacturing. Since the early twentieth century, medicines such as salvarsan, aspirin, and the sulfonamides have represented the ideal of science-based drug development: results of chemists' efforts to purify, structurally characterize, and then synthetically manufacture organic compounds. Yet preparations from biological materials, especially plants, had likely made up the majority of drugs on the market. More recently, historians have begun to address the historiographical imbalance—which has favored synthetic organic chemistry—in order to better reflect the importance of biological research to the design, production, and standardization of pharmaceuticals. Studies have considered the significance of "biologics" as a conceptual category in research and regulation.[15] This article elucidates the Japanese context at midcentury, at precisely the moment when

13. Nihon penishirin gakujutsu kyōgikai kiji (NPGKK) are published records from the JPRA meetings that are based on minutes kept by Yagisawa Yukimasa, the managing director of the JPRA. The records are printed in the JPRA's journal, the *Journal of Penicillin*. Takeda Keiichi, in *Penishirin sangyō kotohajime* [Dawn of the penicillin industry] (Tokyo: Maruzen puranetto, 2007), reproduces large parts of these records with some annotation. Takeda's stated purpose is to draw historians' attention to the records as an important source.

14. On the inseparability of knowledge and institutions, see Christophe Lécuyer, *Making Silicon Valley: Innovation and the Growth of High Tech, 1930–1970* (Cambridge, MA: MIT Press, 2006); Cyrus C. M. Mody, *Instrumental Community: Probe Microscopy and the Path to Nanotechnology* (Cambridge, MA: MIT Press, 2011); Ann Johnson, *Hitting the Brakes: Engineering Design and the Production of Knowledge* (Durham, NC: Duke University Press, 2009); Atsushi Akera, *Calculating a Natural World: Scientists, Engineers, and Computers during the Rise of U.S. Cold War Research* (Cambridge, MA: MIT Press, 2007).

15. Drugs made from living organisms also included vaccines and sera. See, for example, Jean-Paul Gaudillière, "Introduction: Drug Trajectories," *Studies in History and Philosophy of Biological and Biomedical Sciences* 36 (2005): 603–11, and related articles in the issue; and Alexander von

synthetic organic chemistry's overwhelming dominance as the ideal model of pharmaceutical research began to shift. After World War II, governments across the world invested in microbial expertise on an unprecedented scale in order to produce penicillin locally.[16]

I follow developments from the establishment of the JPRA in 1946 to when the focus of the JPRA shifted from penicillin to other antibiotics, signified by its name change to the Japan Antibiotics Research Association (Nihon kōseibusshitsu gakujutsu kyōgikai, JARA) in 1951. I concentrate especially on the first half of this period (up to mid-1948) during which most of the basic problems of domestication were worked out by the JPRA's Central Laboratory. Production-related questions were academic research questions at the scale of the laboratory bench; therefore, how scientists approached them is revealing of the contours of Japanese fermentation expertise.[17] Beyond the transfer of submerged culture fermentation technology for antibiotic mass production, a distinctive engagement with agricultural chemistry's longstanding perception of microbes—as alchemists of the environment, with the ability to transform resource scarcity into productive abundance—organized the knowledge by which penicillin scientists made the domestic environment work, and deeply shaped antibiotic research in the subsequent decades in Japan.

PENICILLIN PRODUCTION IMMEDIATELY AFTER WORLD WAR II

The Japan Penicillin Manufacturing Association (JPMA) was formed in response to a meeting held in July 1946 at the Ministry of Health and Welfare under the directive of GHQ (General Headquarters of the occupation government).[18] There, the Ministry offered clarification concerning GHQ's decision in February to ban the sale of penicillin before issuing manufacturing permits again in May: it was a necessary step toward raising the standards of domestic production, which were unacceptably uneven. It was to this end that the Ministry proposed the formation of two new associations on behalf

Schwerin, Heiko Stoff, and Bettina Wahrig, eds., *Biologics, a History of Agents Made from Living Organisms in the Twentieth Century* (London: Pickering & Chatto, 2013).

16. Robert Bud, *Penicillin: Triumph and Tragedy* (Oxford: Oxford University Press, 2007).

17. On how knowledge created at the laboratory bench is scaled up for mass production in industrial fermentation processes, see Victoria Lee, "Scaling Up from the Bench: Fermentation Tank," in *Boxes: A Field Guide*, eds. Susanne Bauer, Maria Rentetzi, and Martina Schlünder (Manchester: Mattering Press, forthcoming).

18. Nihon penishirin kyōkai, *Penishirin no ayumi* (ref. 1), 19.

of GHQ, the JPMA and the JPRA. In turn, the Ministry promised that GHQ would do what it could to aid the transfer of American technology and invite foreign experts to Japan, as well as offer microbial strains and allow penicillin manufacturers special access to essential materials such as electricity and coal. The occupation authorities thus presented penicillin, like they would also do for the insecticide DDT, as a gift from the United States to Japan.[19]

When American troops, riding in Jeeps, entered Japan to occupy the country after Japan's unconditional surrender in 1945, they encountered a people in exhaustion.[20] Japan had been at war for fifteen years, as Japan's Kwantung Army had invaded Chinese territory in Manchuria in 1931 before full-scale war broke out in China in 1937. Cities had been flattened by firebombing; Hiroshima and Nagasaki, by atomic bombs. The occupation government was headed by General Douglas MacArthur, the Supreme Commander for the Allied Powers (whose administration was often referred to as SCAP, or GHQ for General Headquarters). SCAP arrived with an agenda to implement sweeping reforms and democratize Japan, or in a common phrase of the time, to enforce a "revolution from above."[21] Meanwhile, Japan was cut off from the former empire that had supplied much of its food, and starvation and disease were rife: reports counted 146,241 deaths from tuberculosis in 1947, and 99,654 deaths from other infectious diseases between 1945 and 1948.[22] Trains between Tokyo and the countryside overflowed with crowds in search of food for which they could barter their clothes. As a part of public health policy, the Japanese government set up a series of licensed brothels for American troops to contain the spread of venereal disease (which SCAP at first condemned but eventually allowed), while SCAP had fields sprayed with DDT to kill ticks.

Following the opening meeting of the JPMA on August 15, 1946, the Japan Penicillin Research Association (JPRA) held its own opening meeting soon

19. Christopher Aldous and Akihito Suzuki, *Reforming Public Health in Occupied Japan, 1945–52: Alien Prescriptions?* (Abingdon, Oxon: Routledge, 2012), 101–02.

20. Dower, *Embracing Defeat* (ref. 5).

21. Ibid., 69. The constitution was rewritten in the first years of the occupation, which relegated the emperor from absolute authority to a symbol of the state and forbade the country from going to war, as well as guaranteeing new civil liberties. The push for democratization and demilitarization lasted briefly until the onset of the Cold War. With the Communist victory in China in 1949 and the outbreak of the Korean War (1950–1953), American policy changed to support a conservative order and economic growth in Japan, a trend that would persist beyond the end of the occupation in 1952.

22. Ibid., 103.

after on August 26. In his introductory remarks, Katsumata Minoru (the Chief of the Public Health Bureau of the Ministry of Health and Welfare) assured the scientists attending that the domestication of penicillin production was a matter for which GHQ too held "great concern."[23] The reasons for this concern remained unspoken, but they would have been obvious to those present. Of the first authorized batch of penicillin released by the pharmaceutical firm Banyū Seiyaku in May, a total of 167 bottles all subject to distribution controls, 50 bottles had gone to the Recreation and Amusement Association (the network of brothels set up by the Japanese government in preparation for the arrival of U.S. troops), and 27 bottles had gone to Yoshiwara Hospital in Tokyo's red-light district. As Commanding General of the Eighth United States Army Robert L. Eichelberger remarked, there was more to fear from venereal disease than the atomic bomb.[24] Japan was not alone in this situation; in Europe, Allied forces were prioritizing penicillin for countering syphilis in occupied West Germany.[25] A SCAP pamphlet published by the Public Health and Welfare Section in 1949 explained:

> In planning to provide adequate medical supplies and equipment to meet the needs of the civilian population, *the problem of utmost importance that confronted SCAP was (1) should all needed supplies be imported at the expense of the American taxpayer, or (2) should every effort be made to increase and stimulate indigenous Japanese production* and import only those materials, preferably in raw form, which would not be available in Japanese supply. It was decided that the latter course would be followed and immediate steps were taken to rehabilitate the Japanese medical supply and equipment industry.[26]

At the time that the JPMA and JPRA were established under GHQ's directive, penicillin was already being produced domestically—a remainder from the Japanese wartime project. During the war, based on information in journals delivered from German submarines, scientists at the Army Medical

23. NPGKK I, 57. Here, the Roman numeral refers to the number of the report, while the Arabic numeral refers to the page number within the journal. For further explanation of the records as a source, see ref. 13.

24. Nihon penishirin kyōkai, *Penishirin no ayumi* (ref. 1), 2.

25. Bud, *Penicillin* (ref. 16), 83.

26. General Headquarters, Supreme Commander for the Allied Powers, Public Health and Welfare Section, *Mission and Accomplishments of the Occupation in the Public Health and Welfare Fields* (Tokyo: Supreme Commander for the Allied Powers, 1949), 23 (emphasis added).

School in Tokyo formed the Hekiso Committee ("blue-essence," or penicillin committee) with the aim to industrialize penicillin manufacture by surface culture. At the same time, the eclipse in scientific communication had made researchers hungry for information about new advances abroad. Young researcher Umezawa Hamao later recalled seeing the foreign periodical that would introduce him to penicillin on a desk in 1943, and feeling "like a starving man coming across food."[27] The wartime committee was a large-scale coordination of efforts by prominent scientists, including agricultural chemists with expertise in both microbiology and microbial chemistry, plant physiologists and plant chemists, medical bacteriologists, a synthetic organic chemist, and physicians.[28] The committee developed strains, culture methods, and refinement and assay methods, and approached the confectioners Morinaga and Meiji Seika (the latter was then part of Yamagata Gōdō) as well as the pharmaceutical company Banyū Seiyaku, to begin manufacturing penicillin by surface culture in dairy bottles. Firebombing destroyed factories, but immediately before the surrender, Banyū produced the first batch of 30 grams.

Under occupation, not only was the military disbanded and the large business conglomerates known as the *zaibatsu* targeted for dismantling; all research deemed relevant to military application was banned, surviving facilities were suspended and allocated for reparations, and undertaking any research project required GHQ's permission.[29] The Institute of Physical and Chemical Research's cyclotrons were torched to pieces and dumped in Tokyo Bay in November 1945.[30] Drug stocks, which had been military goods, were confiscated from October 1945, and the Ministry of Health and Welfare took over distribution controls.[31] Penicillin manufacturers slowly repaired facilities, and more firms joined in production. The penicillin produced averaged

27. Umezawa Hamao, *Kōseibusshitsu o motomete* [Searching for antibiotics] (Tokyo: Bungei shunju, 1987), 13.

28. Tsunoda Fusako, *Hekiso—Nihon penishirin monogatari* [Hekiso: Japan's penicillin story] (Tokyo: Shinchōsha, 1978); Hazime Mizoguchi, "Penicillin Production and the Reconstruction of the Pharmaceutical Industry," in *A Social History of Science and Technology in Contemporary Japan, Vol. 2: Road to Self-Reliance 1952–1959*, eds. Shigeru Nakayama, Kunio Gotō, and Hitoshi Yoshioka (Melbourne: Trans Pacific Press, 2005), 551.

29. Nishiyama, *Engineering War and Peace* (ref. 7), 85–104.

30. Dong-Won Kim, "Yoshio Nishina and Two Cyclotrons," *Historical Studies in the Physical and Biological Sciences* 36 (2006): 243–73.

31. Mizoguchi, "Penicillin Production" (ref. 28), 548. The prefectural government authorized pharmacies, clinics, and other dealers to receive rations via a purchasing passbook; Umemura, *Japanese Pharmaceutical Industry* (ref. 3), 35n.35.

29 units per milliliter (u/mL) in 1946 and still under 100 u/mL in 1947. It was so impure that it made patients jump up in pain when injected.[32] The standard unit for penicillin is the Oxford unit, which is defined by a fixed zone of inhibition of bacterial growth in a standard assay. Pure penicillin, for example, contains 1,650 units per milligram (u/mg). GHQ's overall goal was to have penicillin manufactured to the same standard as the U.S. product as quickly as possible, though in the meantime the "working standard" was more relaxed than that of the U.S. Food and Drug Administration.[33] The working standard that domestic manufacturers aimed to meet was 152 u/mg in December 1946.[34]

In promoting the domestication of penicillin production in Japan, SCAP's primary concern was to reduce the cost of the occupation to the American taxpayer, rather than giving priority to protecting intellectual property. Future competition from Japanese industries seemed anything but a likely prospect at the time, and a GHQ Public Health and Welfare Section pamphlet noted that, "due to the lack of raw materials and the deterioration of equipment, the remaining factories were producing only 20% of prewar requirements."[35] The issue of intellectual property goes entirely unmentioned in the regular SCAP publications that summarized the occupation's activities and accomplishments. GHQ's focus was first and foremost on bringing down prices by increasing the quantity of penicillin production, and once mass-quantity production was achieved, on increasing the quality of the penicillin produced to a satisfactory standard. Public Health and Welfare Section publications summarizing achievements for the years 1949 and 1950 celebrate progress in domestic manufacture in terms of the outcome in price reductions as well as the shift in emphasis from quantity to quality improvement, and they delineate the limits of domestic manufacture in terms of continued importation of supplies.[36] The figures included clearly show the dramatic increase in

32. Sumiki Yusuke, *Kōseibusshitsu* [Antibiotics] (Tokyo: Tōkyō daigaku shuppansha, 1961), 162; Nihon penishirin kyōkai, *Penishirin no ayumi* (ref. 1), 19.

33. NPGKK I, 60; NPGKK II, 125; NPGKK III, 189.

34. NPGKK II, 125–28.

35. General Headquarters, *Mission and Accomplishments* (ref. 26), 22.

36. For example: "The calendar year 1949 may be described in summary as a period of transition from postwar activities emphasizing quantity, to a period with primary emphasis on quality improvement" (118); "As a result of the rehabilitation of the pharmaceutical and medical supply industries, the volume of these imports has rapidly decreased, with commensurate savings in the cost of the occupation of the American taxpayer" (121); "Production of penicillin during the year exceeded all expectations . . . The volume of production justified the removal of penicillin

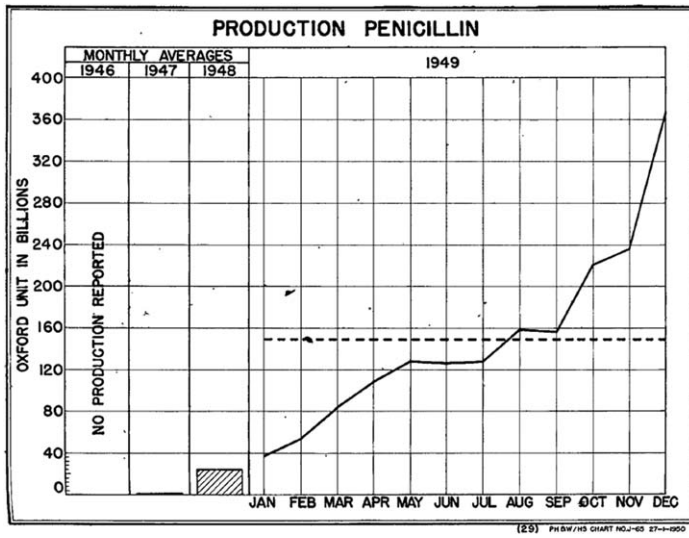

FIG. 1. Graph showing monthly production amounts for penicillin. A dotted line at 152 billion units serves as a reference point for reading production amounts against the working standard, which was 152 units per milligram. *Source:* General Headquarters, *Annual Summary—1949* (ref. 36), 124.

the quantity of domestic penicillin manufacture (Fig. 1) and the decrease in prices (Fig. 2).

Patent rights became an issue only from September 1, 1949, onward, when the Afterwar Remedy Order of the United Nations' Industrial Property came into effect. The law recognized patents registered by United Nations members within the period dating back to one year before the start of the war, and it meant that a number of penicillin producers in Japan who had been manufacturing without licenses would now have to procure a license in order to continue. (Penicillin itself was not patented for humanitarian reasons,

from ration distribution controls in April 1949, and was the causative factor in reducing prices on all penicillin products by approximately 50% as of 1 October. It was necessary to import 125,000 gallons of corn steep liquor for penicillin production during the year" (123); in General Headquarters, Supreme Commander for the Allied Powers, Public Health and Welfare Section, *Public Health and Welfare in Japan, Annual Summary—1949, Volume I* (Tokyo: Supreme Commander for the Allied Powers, 1949). "During 1950, continued advances were realized which have resulted in a product of proven quality with a decided reduction in price, making the Japanese product a factor in international trade" (83); in General Headquarters, Supreme Commander for the Allied Powers, Public Health and Welfare Section, *Public Health and Welfare in Japan, Annual Summary—1950, Volume I* (Tokyo: Supreme Commander for the Allied Powers, 1950).

PENICILLIN PRODUCTION

CY	Units	Units/100,000	Av Price per 100,000 units	Total Value Million/Yen
1946	negligible	--	--	negligible
1947	13,821,390,000	138,214	¥1,333 (offi-	184
1948	297,029,810,000	2,970,298	500 cial)	1,485
1949	1,798,300,177,000	17,983,002	140 "	2,518
1950	7,495,530,385,000	74,955,304	45 (est av)	3,373

FIG. 2. Table showing the dramatic decrease in the cost of penicillin. Data shown in the table is explained in the main text in the source publication: "The value in 1947, 1948, and 1949 is based on official prices established by the Japanese Price Board. In 1950 the price control was removed. Value in 1950 is based on an estimated average price of ¥45 per 100,000 units." *Source:* General Headquarters, *Annual Summary—1950* (ref. 36), 83.

though some of the manufacturing processes were patented.[37]) But until that moment—as the JPMA's institutional history explains—productivity and cooperation between firms in penicillin manufacture had been emphasized over the enforcement of patent rights, in the name of widespread dissemination and application of the drug to patients. This all changed in late 1949, despite an unsuccessful attempt on the part of GHQ's Public Health and Welfare Section to negotiate an exception for penicillin with the U.S. Department of State.[38]

The son of the president of Banyū Seiyaku helped to negotiate an agreement with Bristol, the American pharmaceutical enterprise, for manufacturing the penicillin derivative G procaine in 1953 so that all twenty Japanese producers were able to continue manufacturing penicillin G procaine without conflict over rights.[39] However, as business historian Julia Yongue argues, that would be the last instance of open cooperation between firms in pharmaceutical manufacturing, just as the penicillin boom was ending. A new commercial era began in the 1950s and continued into the 1960s, in which Japanese pharmaceutical firms individually negotiated their own licenses with foreign businesses for technology transfer, and competed with each other in litigation over patents.[40] But by

37. Neushul, "Mass Production of Penicillin" (ref. 2); John Patrick Swann, "The Search for Synthetic Penicillin during World War II," *The British Journal for the History of Science* 16 (1983): 154–90; Nicolas Rasmussen, "Of 'Small Men', Big Science and Bigger Business: The Second World War and Biomedical Research in the United States," *Minerva* 40 (2002): 115–46.

38. Nihon penishirin kyōkai, *Penishirin no ayumi* (ref. 1), 113.

39. Yongue, "American Mass Production Technology" (ref. 3), 224–25. There the JPMA is referred to as the JPA, or Japan Penicillin Association.

40. Yongue, "American Mass Production Technology" (ref. 3).

then, the period of the most crucial developments in the domestication of penicillin production was already over, as the country reached self-sufficiency in penicillin well before the 1949 law came into effect. For the very first antibiotic, penicillin, it was not firm-to-firm licensing agreements that served as the vehicle for technology domestication. Rather, it was the activities of the JPRA.

THE ROLE OF THE JAPAN PENICILLIN RESEARCH ASSOCIATION

The JPRA, as an association of academic researchers, clearly had a role to play as a designated intermediary between government and industry. This made it distinct from the JPMA, which was a private body of firms. Donations from the JPMA and grants from the Ministry of Education funded JPRA research, and a Ministry of Health and Welfare official was appointed to sit in JPRA meetings. On November 1, 1946, at GHQ's Public Health and Welfare Section with Ministry of Health and Welfare officials present, GHQ officials introduced JPRA scientists to Jackson W. Foster from the University of Texas at Austin.[41] Foster was a student of Selman Waksman and had worked at the New Jersey–based pharmaceutical company and penicillin manufacturer Merck during the war. His role as a foreign consultant would be to embody the six years (and $25 million) of American experience in the field, which he said his government had asked him to bring for Japan's "peacetime battle" against disease.[42]

Afterward, GHQ officials issued an outline of objectives to the JPRA.[43] The JPRA's tasks included: establishing a Central Laboratory in order to expand basic research (which would use existing facilities in universities); constructing a submerged-culture pilot tank (which would need to be built anew at a university or research institute); and assessing factories and choosing the most promising ones to support in order to use limited resources effectively. The Ministry of Health and Welfare with GHQ's approval would appoint assistants to direct research in consultation with the Ministry, and those assistants would in turn appoint the heads of each research section in the JPRA. A central assay laboratory would be constructed under the domain of the Ministry of Health and Welfare. The JPRA would consult with GHQ on how to break

41. NPGKK II, 123.
42. Jackson W. Foster, Preface, *Journal of Penicillin* 1 (1946).
43. NPGKK II, 123.

through bottlenecks and strive toward the increase in production that GHQ requested. Twice a month the Central Laboratory would present detailed research reports to GHQ, the Ministry of Health and Welfare, and each laboratory and factory, and twice a month manufacturers would report on the production situation to GHQ.

The Technical Committee was the core of the JPRA's Central Laboratory, and the scientists whom with Foster would work most closely in the following months. It included medical researchers from the University of Tokyo's Institute of Infectious Diseases, such as Umezawa Hamao and Hosoya Seigo, but most of the members were senior researchers from the Department of Agricultural Chemistry in the University of Tokyo's Faculty of Agriculture, such as Yabuta Teijirō, Sakaguchi Kin'ichirō, Asai Takenobu, and Sumiki Yusuke.[44] The committee was more or less the same as that of the wartime project. Sakaguchi, a fermentation expert, would go on to set up the Institute of Applied Microbiology at the University of Tokyo in 1953, while Yabuta, a leading expert on molds, had been the scientist to isolate the first plant hormone gibberellin. A Clinical Committee was also established to collate clinical experiences of penicillin treatment (its members were limited to researchers in state hospitals, since these were the only hospitals receiving penicillin supplies under the distribution controls).

Foster gave a three-day series of lectures in Tokyo, attended by 120 scientists, 6 bureaucrats from the Ministry of Health and Welfare and the Ministry of Education, and 201 representatives of 47 companies from the 51 members of the JPMA, in order to help bring Japan up to date on technical knowledge about penicillin.[45] Later, Foster served as a consultant on submerged culture plant construction, for manufacturers as well as the JPRA. In addition, some of the raw materials required—those which were new, or simply difficult to obtain in late 1940s Japan—were flown over from the United States, put in a Jeep and delivered to the JPRA Central Laboratory's Culture Section (then

44. Formerly Tokyo Imperial University, the University of Tokyo was renamed in September 1947. For more on its Department of Agricultural Chemistry as a center of fermentation expertise, see Victoria Lee, "Mold Cultures: Traditional Industry and Microbial Studies in Early Twentieth-Century Japan," in *New Perspectives on the History of Life Sciences and Agriculture*, eds. Denise Phillips and Sharon Kingsland (Cham, Switzerland: Springer, 2015), 231–52; Kumazawa Kikuo, "Riibihi to Nihon no nōgaku—Riibihi tanjō 200nen ni saishite" [Liebig and agricultural science in Japan—On the occasion of the 200th anniversary of Liebig's birth], *Hiryō kagaku* 25 (2003): 1–60.

45. NPGKK II, 123.

agricultural chemist Sakaguchi's laboratory at the University of Tokyo), where Foster handed them over to scientists on November 19, 1946. These included various strains for surface culture and the Q176 strain for submerged culture, two liters of corn steep liquor, and lactose and phenyl acetate for culture media.[46] Q176 was four to five times more powerful than the Japanese strains under investigation at that point.[47] The tool of induced mutation for creating more strain varieties was also new, and Central Laboratory scientists quickly adopted the technique.[48] GHQ reported that the "latest American scientific literature has been made available and procurement and allocation programs for certain critical raw materials such as phenyl acetic acid, lactose and amyl acetate have been set up."[49]

Section divisions within the Central Laboratory reflected the main research problems involved in penicillin production. The Strains Section focused on screening, or selecting microbial strains most suitable to the task of penicillin manufacture. The Culture Section developed media for mass production that relied on domestic raw materials as much as possible, for *both* surface culture and submerged culture—aiming ultimately for a transition to submerged culture production, but using surface culture to bridge the production gap that would otherwise be caused by the transition. The Refinement Section similarly researched refinement methods. The Central Laboratory was also tasked with building a submerged culture pilot tank, where contamination—the infiltration of miscellaneous microbes that might decrease yield—was an especially challenging problem to solve.

The Assay Section assessed the quality of penicillin produced by manufacturers and officially authorized them. On GHQ's decision, the Assay Section was relocated along with other antibiotic facilities from the University of Tokyo's Institute of Infectious Diseases to the new National Institute of Health (Kokuritsu yobō eisei kenkyūjo, NIH; this Japanese institution had been established early in 1947 and was attached to the Ministry of Health and Welfare).[50] In his lectures Foster had stressed the importance of upgrading the

46. NPGKK II, 125.

47. Sumiki, *Kōseibusshitsu* (ref. 32), 166.

48. NPGKK II, 127.

49. Supreme Commander for the Allied Powers, *Summation of Non-Military Activities in Japan, No. 15, December 1946* (Tokyo: Supreme Commander for the Allied Powers, 1946), 226.

50. Until then, the University of Tokyo's Institute of Infectious Diseases had been assaying its own vaccines. It produced about half of the total Japanese manufacture of vaccines, inoculation materials, and sera. The Kitasato Institute—a private medical laboratory founded by Kitasato

assay method from the dilution method, which was resulting in large errors, to the internationally adopted cup method.[51] But overcoming the limitations of local resources was not a small challenge. One of the main problems was that the cup was supposed to be made of aluminum. The economic conditions meant that scientists had to use instead a cut glass tube, but it was impossible to make the cut part flat, and Assay Section scientists were anxious about this problem even in March 1947, as they were finalizing the draft of an assay method proposal to be sent out to physicians and factory technicians.[52] In December 1946, when the chemical company Yaesu Kagaku managed to produce penicillin at 152 u/mg, the Assay Section noted that it met the working standard.[53]

The JPRA facilitated exchange between academic scientists and experts in the industrial and clinical spheres. The academic scientists in the wartime Hekiso Committee had not included engineering specialists. However, submerged culture production required a new kind of large-scale apparatus—the sterile aerobic fermentation tank—and thus demanded participation from industry, in particular from chemical engineering and heavy chemical firms.[54] Thus it was the JPMA and not the JPRA that was responsible for preparing two sections to develop industrial culturing and refinement equipment.[55] In 1948, the Central Laboratory added two chemical engineers from the Tokyo Institute of Technology to oversee the construction of the JPRA's submerged culture pilot tank and refinement equipment, which in turn would be made

Shibasaburō in 1914—also made sera, but since it was a private laboratory, its biological products had to be approved by the Institute of Infectious Diseases. GHQ found it odd that the same institute that made vaccines had the responsibility of approving them. In the end, GHQ decided that the new Japanese NIH would be responsible for assays, and moved about half of the facilities and members of the Institute of Infectious Diseases there, including the antibiotics section. Umezawa, *Kōseibusshitsu o motomete* (ref. 27), 38–39.

51. NPGKK I, 59. The dilution method involved a series of increasingly diluted samples of the antibiotic placed in media in tubes or plates, inoculating and incubating the samples with an organism, and then deducing the potency of the samples from the decrease in the organism's growth across the series. The cup method involved placing a cup filled with the antibiotic into a solid medium seeded with an organism, incubating it, and then measuring the size of the zone where the organism's growth was inhibited around the cup.

52. NPGKK IV, 252.

53. NPGKK II, 128.

54. NPGKK II, 126; Iijima Takashi, *Nihon no kagaku gijutsu—Kigyōshi ni miru sono kōzō* [Chemical technology in Japan—Its structure as seen in business history] (Tokyo: Kōgyō chōsakai, 1981), 133.

55. NPGKK II, 123.

by Mitsui and Hitachi, respectively.[56] Commercial firms were faster than the JPRA to build submerged culture pilot plants, with the first opening at Tōyō Rayon on March 11, 1947, and others quickly following.[57] JPRA machinery association meetings in Tokyo and Osaka allowed academic scientists and factory technicians to exchange designs and data.[58] In the meantime, JPRA representatives, including a Ministry of Health and Welfare bureaucrat, visited the Acetone Industrial Association in February 1947 to explain their need for solvents for the refinement process.[59] Even by September 1947, however, butanol factories were still idle; the solvent industry would not revive until about the end of the decade.[60] It was as late as June 1948 when the Central Laboratory's full-sized pilot plant came into operation at the NIH, and the refinement methods were upgraded with the latest high-performance machines in the early 1950s.[61]

The JPRA's Clinical Section allowed information from clinical trials to be conveyed back to penicillin manufacturers by way of the Central Laboratory, which was crucial in effecting product standardization, especially after an adequate production quantity of penicillin had been achieved. Physicians conveyed their views on product quality, pricing, and development back to the Central Laboratory's Assay Section via the Penicillin Standards Investigation Committee, with Ministry of Health and Welfare officials involved as intermediaries.[62] In a November 1947 meeting, for example, physicians' concerns included increasing product potency to decrease side effects; limiting penicillin prices to facilitate physicians' turning to penicillin as the first line of treatment; and requesting the development of new forms of penicillin that would maintain the concentration of penicillin in the blood for longer periods after injection. During a December 1947 visit to the factory of one supplier, Meiji Seika, Central Laboratory scientists assured physicians that although previously it had been necessary to focus on quantity over quality, scientists would now be working to solve the problem of side effects, which were

56. Iijima, *Nihon no kagaku gijutsu* (ref. 54), 132–35; NPGKK III, 191.

57. NPGKK III, 192; NPGKK IV, 253; NPGKK VI, 407.

58. NPGKK III, 191–92; NPGKK IV, 255.

59. NPGKK III, 190.

60. NPGKK VIII, 557; Iijima, *Nihon no kagaku gijutsu* (ref. 54), 135.

61. Ōyama Yoshitoshi, "Kagaku kōgaku no riteihyō—3. Kaken to penishirin puranto" [Milestones in chemical engineering—3. Kaken and the penicillin plant], *Shizen* 24, no. 6 (1969): 64; Iijima, *Nihon no kagaku gijutsu* (ref. 54), 134.

62. NPGKK IX, 623.

correlated with refinement methods.[63] Side effects differed with the manufacturer due to varying refinement procedures, and also seemed to depend on the microbial strain used in production.[64]

All of the aspects of production that were under research in the Central Laboratory—strains, culture media, refinement methods, and even assaying procedures—required domestication. Apart from the chemical engineering dimensions that went into building the physical components of mass-production plants (which were largely overseen by the JPMA instead), the intellectual skills for domestication were to be found in the fermentation knowledge that was already existent from wartime, and which carried over directly into postwar JPRA's Central Laboratory because of the continuity in personnel.

The occupation state's successful coordination of *academic* research on the mass production process is notable, rather than leaving the research initiative to firms. The fact that the postwar penicillin project followed fifteen years of war helped this particular organizational configuration to function effectively.[65] Not only were the key researchers largely the same as in the wartime committee; the centralized, state-led coordination of the project, the devotion of prominent university scientists exclusively to one production problem, and state policies that confined industrial possibility to this sector by rationing raw materials and providing other economic incentives were all important parallels between technical projects in Japan before and after 1945.

By contrast, in postwar Italy, for example, the director of the Istituto Superiore di Sanità (ISS) in Rome, Domenico Marotta, as well as the visiting British penicillin scientist, Ernst Chain, held visions for the ISS's penicillin factory that were similar to the function of the JPRA: as a public research establishment, a center for both biochemical and biotechnological innovation, and a service to industry players through its fermentation pilot plant linking laboratory science to manufacturing improvements. It was an important center for a time with results such as the discovery of 6-APA (the basis of

63. NPGKK IX, 625–26. Physicians reported that the incidence of side effects had lessened after the product potency increased from about 300 u/mg in September 1947 to 800 u/mg in December 1947.

64. NPGKK X, 75. According to physicians, there were usually no side effects apart from smarting and fever, but occasional side effects included headache and vomiting. NPGKK III, 190. At a February 1948 meeting, physicians reported that about 30% of patients experienced side effects from injection of penicillin into the muscle. NPGKK X, 75.

65. See, for example, Mimura, *Planning for Empire* (ref. 10); Mizuno, *Science for the Empire*, 47–49 (ref. 10).

semisynthetic penicillins). However, after Chain left in 1961, the liberal protectionist climate of postwar Italy changed. The ISS's production component fared badly, and Marotta was prosecuted and attacked for corrupting the ISS's public health mission.[66]

Reasons for the flourishing of the JPRA (and then the JARA) also lie in the longer history of Japanese fermentation research. Functionally, as an academic intermediary between government objectives and industrial production, it was comparable to the national and regional experiment stations (*shikenjo*) that were set up by Japanese government ministries from the end of the nineteenth century to aid small and medium-sized enterprises. Like the JPRA, this network of institutions was a state-supported information mechanism to facilitate novel technology domestication and raise the competitiveness of domestic businesses, via laboratory research on manufacturing processes and industrial surveys.[67] The experiment stations employed scientists from the universities and technical colleges. For both academic and industrial scientists in fermentation-related fields, such institutions were familiar precedents for the kind of state-backed research coordination on commercial production problems that the JPRA represented.

APPROACHES TO PRODUCTION PROBLEMS AT THE CENTRAL LABORATORY

From the beginning, JPRA scientists carrying out "general and basic research on penicillin" indicated that along with achieving the penicillin production objectives, they wanted to do research of their own free direction.[68] At the first meeting of the Strains and Culture Sections, assignments included not only penicillin-related topics such as submerged culture, surface culture, and increasing the power of strains, but also looking for strains outside of the blue mold that would produce antibiotics, and investigating strains that would

66. Mauro Capocci, "'A Chain is Gonna Come.' Building a Penicillin Production Plant in Post-War Italy," *Dynamis* 31 (2011): 343–62.

67. Tessa Morris-Suzuki, *The Technological Transformation of Japan: From the Seventeenth to the Twenty-First Century* (Cambridge: Cambridge University Press, 1994), 98–103; Kaoru Sugihara, "The Development of an Informational Infrastructure in Meiji Japan," in *Information Acumen: The Understanding and Use of Knowledge in Modern Business*, ed. Lisa Bud-Frierman (London: Routledge, 1994), 75–97; Lee, "Mold Cultures" (ref. 44).

68. NPGKK I, 57.

produce antitoxins.[69] At the same time, they held a pragmatic view of the local industrial conditions. Both they and Foster knew that material limitations would compel Japanese firms to continue surface culture production for many months, even though submerged culture would ultimately achieve the necessary step-up in production quantities. Because of this, JPRA scientists developed strains and culture media for both production methods in parallel.

The French wartime penicillin project offers an illuminating contrast because of the existence of comparable microbiological skill, at the same time as there were differences in the precise nature of that microbiological knowledge. As in Japan, penicillin development in France was led by academic research rather than firms, namely by medical microbiologists at the Pasteur Institute under a military administration. Scientists in the French project possessed a configuration of expertise similar to the scientists in the Japanese project (though the Japanese team had more chemical expertise), with a biological emphasis on strains, culturing, and assays. Moreover, since the Pasteur Institute was also a vaccine and serum factory, microbiologists were keen to extend the technological possibilities of biological production. However, the French microbiologists' excitement about scientifically advanced biotechnology meant that they pushed for taking the many more months required to build a submerged culture plant, whereas the military engineers disagreed about time and built a surface culture plant without the microbiologists' support. In the end, production failed to materialize before the end of the war, and penicillin production was simply undertaken by the private sector after the war through licensing agreements.[70] Japanese microbiologists in the discipline of agricultural chemistry, on the other hand, had had the wartime experience of developing production technologies for resource-intensive goods such as fuel alcohols, which was one reason behind their sensitivity to economic constraints in industry when undertaking the postwar project.[71]

Moreover, in the pre–World War II period, Japanese agricultural chemists had developed ways of approaching microorganisms that would become significant in both the theoretical and applied spheres. For historian Robert Bud, the accumulation of know-how in applied science through early research on organic acid fermentations, at the German University in Prague and the New

69. NPGKK I, 59.

70. Jean-Paul Gaudillière and Bernd Gausemeier, "Molding National Research Systems: The Introduction of Penicillin to France and Germany," *Osiris* 20 (2005): 180–202.

71. Victoria Lee, "The Arts of the Microbial World: Biosynthetic Technologies in Twentieth-Century Japan" (PhD dissertation, Princeton University, 2014).

York firm Pfizer, was a key factor in the success of the Anglo-American penicillin program.[72] Interwar Japanese microbiological research within agricultural chemistry at Tokyo Imperial University (later the University of Tokyo) is a revealing comparison because this work, too, focused heavily on organic acid fermentations of *Aspergillus* and other molds, having expanded from studies of the molds used in traditional sake and soy-sauce brewing. However, from the 1920s, the research was deliberately theoretical rather than practically oriented—aimed at understanding the biochemistry of the mold, and without links to breweries or other industrial spaces.[73]

Whereas Bud characterizes the work at Prague as part of "a low status but industrially well-connected network," the Japanese interwar work in organic acid fermentations differs in being moderately high status and distant from industry.[74] Its distance from industry meant that the Japanese work did not produce the innovations in submerged culture fermentation that the German work produced, which would later prove critical to penicillin manufacture. But the subsequent rapid domestication of penicillin and antibiotic research in Japan indicates that there were aspects other than submerged culture at the heart of antibiotic production and innovation, namely, a biological approach to microbes and a sense for what microbes were able to do. The implications of Japanese fermentation scientists' approach can be seen especially in screening work—the task of selecting microbes suitable for use in mass production of a metabolite (a substance formed as a result of biochemical processes in a cell).

Scientists indicated that they did not see screening work as entirely routine. At meetings there were steady reports of work on new antibiotics, although they were often not given priority and came after reports on penicillin work. There was research on antibiotics produced by actinomycetes, *Penicillium*, and *Aspergillus candidus*, for example, as well as gramicidin from a *B. brevis* soil microbe, and streptomycin-lookalike compounds from actinomycetes strains.[75] In order to select strains, one researcher in the Strains Section

72. Robert Bud, "Innovators, Deep Fermentation and Antibiotics: Promoting Applied Science Before and After the Second World War," *Dynamis* 31 (2011): 323–42.

73. Sakaguchi Kin'ichirō, "Michi e no gunzō" [Portrayal of a group toward the unknown], in *Hakkō to shugaku* [Fermentation and liquor science] (Tokyo: Iwanami shoten, 1998), 191–208; Teizo Takahashi and Kin-ichiro Sakaguchi, *Summaries of Papers* (Tokyo: Committee of Commemorative Meeting of 35 Year's Anniversary of Professor Kin-ichiro Sakaguchi, 1958).

74. Bud, "Deep Fermentation and Antibiotics" (ref. 72), 332.

75. NPGKK II, 12; NPGKK II, 127; NPGKK III, 189; NPGKK VII, 485.

reported, it was necessary not only to be systematic but also to see the physiological characteristics as important, and to use culture media that would make the physiological differences easy to see.[76]

Such consciousness of the variability and diversity of microbes as biological organisms, each with their own biochemical and physiological capacities, suggests that scientists drew on prior practices in the discipline of agricultural chemistry.[77] It helps to explain the vibrancy and rapid outcomes of JPRA research on antibiotic-producing strains, whether directed toward applied goals for penicillin production or toward gaining knowledge of microbial physiology and ecology more broadly through antibiotic research. On March 20, 1948, Central Laboratory scientists announced that from then on, they would not prepare particular shared topics of research, and instead, the laboratories would simply communicate with each other while doing their own research individually; this marked a point when laboratory research on penicillin was mostly complete.[78] Yet the JPRA's Culture Section—with diligent adherence to JPMA firms' requests—continued to give a long report on strain research for penicillin, and a new mutant strain of Q176 that would produce colorless as opposed to yellow penicillin, which interested the industry side.[79] In June 1948, research on bacterial acquired resistance to penicillin and streptomycin as a laboratory (not clinical) phenomenon came first in the list of research reports.[80] Thus interest in antibiotic resistance in the laboratory context *preceded* the wide occurrence of antibiotic resistance in the clinical context, which was to emerge in the next decade.

JPRA scientists possessed a strong sense of what materials were available or not in Japan, making painstaking comparisons of U.S. and Japanese products, and not only because GHQ had instructed them to do so in their list of directives. During the war, agricultural chemists had done similar work to reconcile manufacturing technologies and natural resources when developing alcohol production for fuels.[81] Investigations of the culture medium for surface culture to produce a higher potency broth took up much of the Central Laboratory's energies until late in 1947. As University of Tokyo agricultural chemist Sumiki Yusuke later described, developing the best culture medium

76. NPGKK XI, 146.
77. Lee, "Mold Cultures" (ref. 44).
78. NPGKK XI, 146.
79. NPGKK XII, 336–38.
80. NPGKK XIII, 413.
81. Lee, "Arts of Microbial World" (ref. 71).

was a messy craft that could be accomplished only by trial and error, since it was impossible to grasp the conditions of every strain growing upon every culture medium and affected by many factors.[82] Importing materials to use in the culture medium was not appealing, and so scientists attempted to investigate nitrogen sources other than corn steep liquor and peptone, and carbon sources other than lactose.

The hunt for a substitute for the corn steep liquor as a nitrogen source included tests of pupae, rice lees, the side products of Japanese brewing industries, and many other chemicals.[83] From early on, soybean was tested as a medium alongside the other standard media.[84] All kinds of ingredients for testing appear in the records of the Culture Section for the years of 1946 and 1947: burdock, rabbit bone, *gomame*, whole dried sardines, potatoes, taro, onion, and *nattō* are only some of them, and this was for surface culture, which was only a temporary means of penicillin production.[85] At a meeting of the Culture Section on June 20, 1947, the group announced that experiments concerning surface culture were largely complete, and they would proceed to research on submerged culture.[86] Even in a new political environment where autarky was not a necessity, JPRA scientists' approaches to the problem of penicillin production drew on autarkic experiences from the wartime period.

In a manner comparable to the centralized, interdisciplinary institutions of the wartime era, the JPRA facilitated exchange of results among many scientists, which was especially useful for problems as highly specific as the culture broth. In one meeting, for example, the explanation for a particularly good culture result ran as follows:

> Of the three types of waste fluid produced by the textiles factory, the secondary product of waste hot water is the best, and it is good to add starch saccharifier (glucose conversion 1%) to it. As for the waste hot water culture broth, do not undertake high-pressure sterilization; in this climate, especially in summer, carry out low-temperature drying. If one adds the P substance donated by Foster, then the potency increases and will remain so for a long time.[87]

82. Sumiki, *Kōseibusshitsu* (ref. 32), 177.
83. NPGKK II, 126.
84. NPGKK II, 125.
85. NPGKK IV, 253.
86. NPGKK VI, 407.
87. NPGKK II, 127.

Along these lines, the best culture media were trial-and-error outcomes for which there was no systematic or rational formula, and so were an area where information exchange was particularly valuable. That such information was openly shared among laboratories was striking, since manufacturing data would normally be closely guarded for commercial products.[88]

The refinement process for penicillin was a similarly messy procedure to improve.[89] Scientists tested the two methods of carbon adsorption and solvent extraction for the products of each company. Most of all, they were concerned about the limited supply of the solvents needed for the extraction method. They sought substitutions for the ammonium sulfate required in the butanol extraction method, and tried butyl acetate as a replacement for amyl acetate.[90] In June 1947, scientists were still worrying about local resources. If the acetone supply was insufficient, they needed a method without acetone, and if butyl acetate was hard to attain, they needed a substitute; it was necessary to investigate alternatives systematically.[91]

One of the most punishing problems in submerged penicillin fermentation was contamination, which could be addressed by keeping the tank environment sterile with the utmost care. The degree to which it affected yield was new to the fermentation industries worldwide.[92] On March 15, 1947, before he left Japan, Foster reiterated to the JPRA the importance of solving the contamination problem whatever the cost in terms of money and time.[93] Like elsewhere, this would eventually be addressed as an engineering problem of sterilizing the tank components and air supply—but in their early studies, Central Laboratory researchers also tried to draw on the knowledge that the agricultural chemists possessed on traditional brewing. At one point, medical bacteriologist Hosoya Seigo of the University of Tokyo's Institute of Infectious Diseases investigated substances such as monoiodoacetic acid that might prevent the action of penicillin-decomposing enzymes coming from

88. Komagata Kazuo (Professor Emeritus, Faculty of Agriculture, University of Tokyo), interview by author, Tokyo, Japan, 8 Jul 2012.

89. Sumiki, *Kōseibusshitsu* (ref. 32), 226.

90. NPGKK II, 125.

91. NPGKK VI, 406.

92. Tanaka Hideo, "Hakkōsō, baiyō sōchi" [Fermenters and bioreactors], in *Hakkō kōgaku 20 seiki no ayumi—Baiotekunorojii no genryū o tadoru (Seibutsu kōgakkaishi tokubetsu gō)* [History of fermentation engineering in the 20th century—Following the origins of biotechnology {Special issue of the journal of the Society for Biotechnology, Japan}], ed. Nihon seibutsu kōgakkai (Osaka: Nihon seibutsu kōgakkai, 2000), 27.

93. NPGKK IV, 254.

contaminating bacteria in the air.[94] Counteracting contamination within the culture medium, instead of preventing contact with contaminating microbes entirely, had resonance with brewing practices of sake and soy sauce in which lactobacilli were deliberately allowed to acidify the broth to make it a more unfavorable environment for the growth of other microbes.

As in Germany, pharmaceutical companies in Japan had historically concentrated on chemical synthesis as the methodological path to novel drug innovation.[95] But even if some large Japanese pharmaceuticals might have hesitated to invest in fermentation and hoped instead to create a competitive niche for themselves in penicillin synthesis, they would have been marginalized in penicillin development, due to GHQ's institutional organization of the domestication project under the JPRA.[96] For chemical firms across a whole range of sectors from textiles to steel, penicillin offered a means to revive at a time when raw materials were scarce, military procurements had vanished, and GHQ rationing policies encouraged development exclusively in penicillin.[97] The scope of incentives for penicillin production went beyond inexpensive bottle (surface culture) fermentation and the more technologically demanding submerged culture fermentation, to the manufacturing of solvents for the refinement process and machinery components. Academic scientists on behalf of the state directed research and issued advice to companies—initially under the Hekiso Committee in wartime, and then the JPRA in the occupation era.

The prominent role played by agricultural chemists in the JPRA ensured *both* microbiological and chemical expertise, facilitating rapid assimilation of the new antibiotic fermentation technologies. This was unlike the situation in Germany, where penicillin research was similarly coordinated by state managers, and yet the leading initiative was left to chemists in pharmaceutical firms as well as powerful academic chemists in a consultancy relationship to them. In the case of the pharmaceutical firm Schering and the Kaiser Wilhelm Institute–based biochemist Adolf Butenandt, both favored the strategy of building upon prior expertise to develop a commercial niche in chemical synthesis, given submerged culture fermentation's technical difficulties, and other factors such as the division of Berlin (where Schering and Butenandt

94. NPGKK II, 127.

95. Nihon yakushi gakkai, ed., *Nihon iyakuhin sangyōshi* [The drug industry in Japan] (Tokyo: Yakuji nippōsha, 1995), 97.

96. Takeda, *Penishirin sangyō kotohajime* (ref. 13), 256–57.

97. Ōyama, "Kagaku kōgaku no riteihyō" (ref. 61), 60–67.

were located), which impeded the transfer of information regarding new technologies. The synthetic venture failed, and in the end, German pharmaceutical firms simply imported American submerged culture technology through patent licensing agreements.[98]

ANTIBIOTIC SCIENCE AFTER PENICILLIN

In October 1948, the Clinical Section revised its penicillin user manual to reflect the changes in product supply and quality: from under 10,000 units per bottle (which set the dose) in November 1947, to 100,000 units per dose, and whereas previously physicians could use penicillin instead of sulfa drugs only for the most serious cases, now it was possible to use penicillin more generally.[99] In June 1948, JPRA physicians had noted *Staphylococcus aureus* resistance to penicillin in a patient for the first time.[100] The problem of antibiotic resistance would only become more serious. Nonetheless, by 1950, production was so ample that physicians began to discuss using penicillin for the prevention rather than treatment of human disease. A series of clinical trials were conducted, focusing on prostitutes as testing subjects and potential users, which lasted for three years in several urban centers across Japan.[101] At the time, physicians dismissed worries about provoking "unconfirmed" antibiotic resistance phenomena in favor of practical need. Central Laboratory microbiologists had already encountered antibiotic resistance as a laboratory phenomenon and understood microbes as part of a wider ecology, but physicians in this period were more likely to take a militaristic approach that aimed to eradicate infection in patients due to their need to deal with immediate problems of illness on a day-to-day basis; this was similar to the British hospital context of the 1950s.[102]

Leaving behind the focus on penicillin, in October 1948, the JPRA's *Journal of Penicillin* became the *Journal of Antibiotics*, and in January 1951, the Japan Penicillin Research Association changed its name to the Japan Antibiotics

98. Gaudillière and Gausemeier, "Molding National Research Systems" (ref. 70).

99. NPGKK XV, 66; NPGKK IX, 623.

100. NPGKK XII, 336.

101. NPGKK XXVI, 747.

102. Flurin Condrau and Robert Kirk, "Negotiating Hospital Infections: The Debate Between Ecological Balance and Eradication Strategies in British Hospitals, 1947–1969," *Dynamis* 31 (2011): 385–406.

Research Association (JARA).[103] The 1949 Afterwar Remedy Order of the United Nations' Industrial Property prompted a shift to more restricted producer participation in which only firms that procured licenses could undertake antibiotic manufacturing. As historian Julia Yongue argues, this marked a shift from a business atmosphere of cooperation, to one of competition and patent litigation between antibiotic-producing firms.[104] For the JPRA, on the other hand, the change meant that the academic association stepped back from the front-seat role it had previously taken in directing developments in the antibiotic industry. In 1949, Japan imported the new antibiotic streptomycin through similar mechanisms to penicillin—that is, through GHQ coordination and JPRA research on domestication—but unlike for penicillin, only a handful of firms obtained a license to manufacture streptomycin.[105]

In the subsequent decades, beginning with a procurement boost from the Korean War and continuing far beyond it, the antibiotic industry flourished in Japan. A diverse array of antibiotics—including both new drugs discovered domestically and imitations of foreign products developed under the process-based patent system—came to market and were prescribed frequently. The high consumption of a variety of antibiotics created the widespread emergence of resistant strains of bacteria, which were often resistant to multiple antibiotics at once.[106] With each appearance of strains resistant to an antibiotic came further therapeutic and commercial incentives to search for new antibiotics. Research on antibiotics took place both in company laboratories, and in academic medical institutions including the antibiotics section at the NIH and the Kitasato Institute.[107] Although Japanese pharmaceutical companies did acquire numerous licenses for antibiotic production from foreign companies, many new drugs were also produced by Japanese companies following discovery and development in Japanese academic laboratories.[108]

103. NPGKK XV, 637; NPGKK XXXIII, 275.

104. Combined with the falling price of penicillin due to competition, the change saw JPMA membership dip from its peak of 72 firms in 1946, to 19 in 1951, and the closure of the JPMA by 1961, even though the JARA continued to exist; Yongue, "American Mass Production Technology" (ref. 3), 224–25.

105. Umemura, *Japanese Pharmaceutical Industry* (ref. 3), 39.

106. Ryochi Fujii, "Changes in Antibiotic Consumption in Japan during the Past 40 Years," *Japanese Journal of Antibiotics* 37 (1984): 2261–70.

107. On antibiotic research at the NIH, see Umezawa, *Kōseibusshitsu o motomete* (ref. 27), 38–39.

108. A few examples include kanamycin, discovered at the Institute of Applied Microbiology at the University of Tokyo and commercialized by Kyōwa Hakkō; bleomycin, discovered at the

In the context of the country's economic growth in the 1950s and 1960s, screening work in laboratories could be seen as exploiting low-cost, intensive scientific labor.[109] Yet, to Japanese microbiologists, screening was not routine. Rather, designing a suitable screening system required synthesizing chemical and microbiological knowledge across fields, and appreciating the variety of microbial physiology and ecology.[110] Historian María Jesús Santesmases's account of 1950s antibiotic screening in the Spanish firm CEPA (Compañia Española de Penicilinas y Antibióticos) offers a number of reasons for why screening is sometimes portrayed as a routine task.[111] One is the hierarchical international division of labor: the American firm Merck outsourced the screening program to CEPA, which took instructions, training, and equipment from Merck. Another is the scale of the program involving tens of thousands of strain samples each year, and its systematic nature whereby the order of individual test procedures and even the target output rate could be standardized like a "testing assembly line."[112] The original aspects of the work tended to be kept hidden or low-profile as commercial secrets, and moreover CEPA antibiotic researchers tended to be bound to that firm's laboratory over their careers.

All of these reasons mean that it is easy to overlook the contribution of such elements as knowing which microbes to screen and the design of the screening system. In Japan, the intellectual and integrative dimensions of antibiotic screening would become institutionally recognized in the decades after the domestication of penicillin production. Unlike in the United States, antibiotic screening was a problem whereby a researcher could earn a PhD degree.[113]

Institute of Microbial Chemistry and commercialized by Nippon Kayaku; and avermectin, developed at the Kitasato Institute and commercialized by Kyōwa Hakkō.

109. J. W. Foster, "A View of Microbiological Science in Japan," *Applied Microbiology* 9 (1961): 445; Umemura, *Japanese Pharmaceutical Industry* (ref. 3), 71. Compare María Jesús Santesmases, "Gender in Research and Industry: Women in Antibiotic Factories in 1950s Spain," in *Gendered Drugs and Medicine: Historical and Socio-Cultural Perspectives*, eds. Teresa Ortiz-Gómez and María Jesús Santesmases (Farnham, Surrey, UK: Ashgate, 2014), 72.

110. Satoshi Omura, "Philosophy of New Drug Discovery," *Microbiological Reviews* 50 (1986): 259–79.

111. María Jesús Santesmases, "Screening Antibiotics: Industrial Research by CEPA and Merck in the 1950s," *Dynamis* 31 (2011): 407–28; Santesmases, "Gender in Research" (ref. 109), 61–84.

112. Santesmases, "Screening Antibiotics" (ref. 111), 413.

113. Foster, "View of Microbiological Science" (ref. 109), 446.

Medical microbiologists and agricultural chemists had come to share common intellectual approaches—such as to antibiotic screening—as a result of working together in the Hekiso Committee and then the JPRA. The disciplinary lines were also sometimes blurred for particular individuals (for example, Sumiki Yusuke was both an agricultural chemist and an antibiotic scientist). Even when research activities in corporate laboratories took more prominence from the 1950s and 1960s, the occupation-era JPRA served as a precedent for later interdisciplinary academic institutions, allowing scientists to engage simultaneously with practical problems and broader microbiological research questions. The establishment of the University of Tokyo's Institute of Applied Microbiology in 1953, for example, created a central space that brought together researchers from across the disciplines of agriculture, engineering, science, and medicine, including in the antibiotic field.[114] Such institutions propagated intellectual approaches to antibiotic research that were legacies of the domestication of penicillin production in the JPRA—and which were, in turn, rooted in fermentation expertise from the wartime and prewar periods.

CONCLUSION

Chemical engineers would often remark tongue-in-cheek that penicillin was "a medicine for companies, not a medicine for people."[115] Yet, companies themselves did not take the lead in directing the Japanese domestication of penicillin production, and therefore a focus on firm-to-firm technology transfer alone would miss the scientific aspects of the process. This was especially the case at a time when government authorities prioritized raising the country's overall production capacity over the enforcement of intellectual property rights. Exploring the critical research role of the interdisciplinary academic association that was the JPRA reveals the specific challenges of domestication, and how

114. Komagata, interview (ref. 88); Tōkyō daigaku ōyō biseibutsu kenkyūjo, ed., *Jūnen no ayumi: 1953–1963* [Ten years' history: 1953–1963] (Tokyo: Tōkyō daigaku ōyō biseibutsu kenkyūjo, 1964). Similarly, research associations modeled on the JPRA, where scientists from different sites in academia, government, and industry shared results and which were supported by funding from state ministries, came to play an important role in the development of other fields beyond antibiotic science; Takehiko Hashimoto, "Technological Research Associations and University-Industry Cooperation," in *Historical Essays on Japanese Technology*, by Takehiko Hashimoto (Tokyo: University of Tokyo Center for Philosophy, 2009), 193–99.

115. Ōyama, "Kagaku kōgaku no riteihyō" (ref. 61), 61.

academic traditions mattered—both institutionally and intellectually—in providing a source of creativity to address those challenges. The fact that penicillin domestication occurred relatively rapidly and smoothly, by coordinating academic research on production problems through an interdisciplinary association that mediated between the demands of government policy and industrial practitioners, suggests that the JPRA's distinctive functioning relied on organizational precedents in pre–World War II as well as wartime fermentation research. Indeed, the personnel in the wartime Hekiso Committee were largely the same as those in the Technical Committee of the JPRA's Central Laboratory. This article's examination of the occupation period preceding Japan's high-growth era and its concomitant expansion of corporate laboratories, then, highlights the ways in which indigenous expertise shaped the postwar development of antibiotic science in Japan.

With the growth of antibiotic mass production, fermentation approaches to microbial research became prominent in the medical and industrial fields of antibiotic science, whether in company or academic laboratories. During penicillin domestication, academic scientists in the Central Laboratory of the JPRA pursued immediate practical problems for industry and broader, longer-term research questions simultaneously. It was not only the existence of microbiological expertise itself but the *kind* of microbiological expertise that was specific to Japan, which blurred the lines between "pure" and "applied." The configuration of expertise contrasts with that in the French wartime penicillin project, where the microbiologists involved did not share the military's sensitivity to economic limitations in manufacturing, as well as with the prewar Prague-centered "applied science" fermentation knowledge, which later became important in Anglo-American penicillin production and which was less engaged with theoretical questions. The microbial engineering expertise showcased in the Prague example became significant globally for antibiotic science after World War II, but what was also important in antibiotic science and often overlooked was a biological approach to microbes and a sense for what microbes were able to do. In addressing the intellectual problems of penicillin domestication—from strain development for both surface and submerged culture, to the investigation of culture media, refinement methods, and contamination countermeasures—Central Laboratory scientists drew on fermentation approaches from the discipline of agricultural chemistry, seeing microbes as a way to manufacture essential chemicals locally in conditions of resource scarcity. The bounty of their scientific toolbox resulted from a historic *perception* of the salience of resource scarcity in motivating experimentation,

and they made the domestic environment work by concentrating on microbes' various physiological and ecological capacities to transform it.

Thus microbiologists would later speak of antibiotics as gifts not from the occupation state, but from the microbes themselves.[116] Between 1947 and 1983, the average life expectancy at birth in Japan rose from 50.05 years for men and 53.96 for women to the highest in the world at 74.20 years for men and 79.78 for women, while the infant mortality rate dropped from 76.7 per 1,000 births to the lowest in the world at 6.2 per 1,000 births.[117] The wide availability and consumption of a multiplicity of antibiotics contributed to this transformation. It also provoked the pervasive incidence of resistant strains, to which scientists responded with more antibiotics even as they studied the mechanisms of resistance. Once attention to antibiotic discovery had receded in Europe and North America, Japan became one of the main centers that continued to produce advances in this field. The industrial view of microbes as an abundant source of new antibiotics, and the clinical view of microbes as resistant pathogens to be fought, fed upon each other. Historian Edmund Russell's observation on pesticides is equally apt for antibacterials: "war and control of nature coevolved: the control of nature expanded the scale of war, and war expanded the scale on which people controlled nature."[118] In the aim to preserve human life by pitching microbes against other microbes, the interactions between agricultural science and medicine in World War II and occupation-era Japan created a simultaneous vision of militaristic control and eradication, and beneficent variety and innovation.

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116. Research Center for Biological Function, The Kitasato Institute, ed., *"Splendid Gifts from Microorganisms": The Achievements of Satoshi Ōmura and His Collaborators*, 2nd ed. (Tokyo: The Kitasato Institute, 1998).

117. Fujii, "Changes in Antibiotic Consumption" (ref. 106), 2261.

118. Edmund Russell, *War and Nature: Fighting Humans and Insects with Chemicals from World War I to Silent Spring* (Cambridge: Cambridge University Press, 2001), 2. With thanks to Nina Lerman and Paul Milazzo for drawing my attention to this connection.

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