NATIONAL ACADEMY OF SCIENCES

# OTTO KRAYER

*1899—1982*

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*A Biographical Memoir by*

AVRAM GOLDSTEIN

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*Biographical Memoir*

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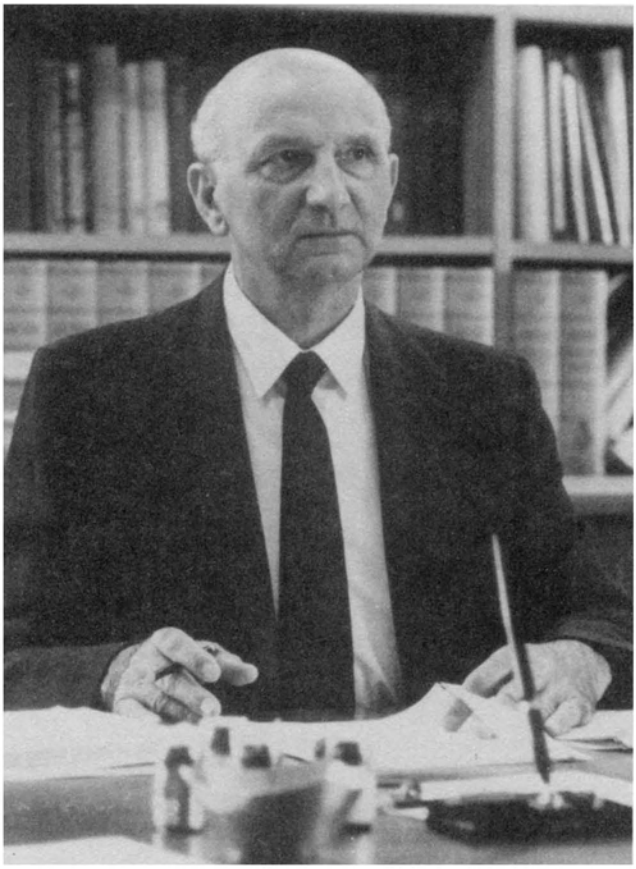

Otto Krayer.

# OTTO KRAYER

*October 22, 1899–March 18, 1982*

BY AVRAM GOLDSTEIN

*Sie können eigentlich nur Solche brauchen, die sich brauchen lassen.*

Schopenhauer. Neue Paralipomena §676,
*Handschriftlicher Nachlass,* Vol. 4 (Leipzig: P. Reclam, 1930).

*For the style is the man, and where a man's treasure is there his heart, and his brain, and his writing, will be also.*

A. Quiller-Couch, *On The Art Of Writing*
(London: G. P. Putnam's Sons, 1916).

In your letter of 15 June you state that you feel the barring of Jewish scientists is an injustice, and that your feelings about this injustice prevent you from accepting a position offered to you.

You are of course personally free to feel any way you like about the way the government acts. It is not acceptable, however, for you to make the practice of your teaching profession dependent upon those feelings. You would in that case not be able in the future to hold any chair in a German university.

Pending final decision on the basis of section 4 of the Law on the Restoration of the Professional Civil Service, I herewith forbid you, effective immediately, from entering any government academic institution, and from using any State libraries or scientific facilities.

THIS REMARKABLE LETTER, dated 20 June 1933, and here reproduced in its entirety, was from the Prussian Minister for Science, Art, and National Education. The recipient, Otto Krayer, who died 18 March 1982, at the age of eighty-two, will be remembered for many things—his outstanding research contributions to cardiovascular pharmacology, his intensely enthusiastic teaching style, his very high standards of scientific publication and editorship, his guidance and support of the many young scientists who came under his influence and went on to significant careers in pharmacology or physiology. Krayer's unique contribution, however, was the example he set in ethical behavior—behavior that in his thirty-fifth year and in the flowering of a promising career brought upon him the full retribution of the Nazi hierarchy.

Robert Jungk, in his book *Brighter Than A Thousand Suns, A Personal History of the Atomic Scientists,*[1] writes about those days in early 1933 in Göttingen: "Only a single one of Göttingen's natural scientists had the courage to protest openly against the dismissal of the Jewish savants. This was the physiologist Krayer. He did not allow himself to be intimidated either by his own dismissal, which was then ordered by the new Prussian Minister of Education, Stuckart, or by the threat of being debarred from employment for the rest of his life."

Yet rare though it was for a non-Jewish German intellectual to jeopardize his own future for the sake of a moral principle, "protest openly" is certainly not accurate. That was not Krayer's style. Never a political activist—nor an organizer or preacher for causes—Krayer would have been the last to condemn his colleagues who, with various rationalizations,

[1] Robert Jungk, *Brighter Than A Thousand Suns, A Personal History of the Atomic Scientists* (New York: Harcourt, Brace and Company, 1958), p. 36.

accepted the evil situation as beyond their control. Krayer believed, very simply, that a person had to do what their conscience said was right, that in such matters it was not a question of weighing consequences. His letter of 15 June 1933, which so infuriated the Nazi bureaucrat, is poignant testimony to this belief. He explains why he cannot accept the proffered appointment to the chair of pharmacology at Düsseldorf—the chair from which the Jewish incumbent Philipp Ellinger had just been removed:

> . . . the primary reason for my reluctance is that I feel the exclusion of Jewish scientists to be an injustice, the necessity of which I cannot understand, since it has been justified by reasons that lie outside the domain of science.
>
> This feeling of injustice is an ethical phenomenon. It is innate to the structure of my personality, and not something imposed from the outside. Under these circumstances, assuming such a position as the one in Düsseldorf would impose a great mental burden on me—a burden that would make it difficult to take up my duties as a teacher with joy and a sense of dedication, without which I cannot teach properly.
>
> I place a high value on the role of university teacher, and I myself would want the privilege of engaging in this activity to be given only to men who, apart from their research capabilities, also have special human qualities. Had I not expressed to you the misgivings that made me hesitate to accept your offer immediately, I would have compromised one of these essential human qualities, that of honesty.
>
> It seems to me, therefore, that the argument that in the interests of the task at hand I must defer my personal misgivings, is an empty one. I would not place even a lesser task in the hands of someone who cannot remain true to himself. Moreover, it is clear to me how great is the responsibility that you have to carry—a responsibility that gives you the right to expect honesty.
>
> The work to which I have heretofore dedicated all my strength, with the goal of applying my scientific knowledge and research expertise to effective university teaching, means so much to me that I could not compromise it with the least bit of dishonesty.
>
> I therefore prefer to forego this appointment, though it is suited to my inclinations and capabilities, rather than having to betray my convic-

tions; or that by remaining silent I would encourage an opinion about me that does not correspond with the facts.

A moral dilemma arises when the policies of a legitimately constituted authority are morally unacceptable. Resistance to a tyranny that can make no claim to a popular mandate is difficult and risky enough. But Hitler's regime had all the trappings of legitimacy, it had come to power in a constitutional manner, and its support went deep and wide among the German people, not excluding the university faculties and students. Noncompliance, under such circumstances, requires the courage of one's convictions to an extraordinary degree. One's support has to come principally from one's own conscience, while one's peers, by and large, tend to distance themselves, in order to avert unpleasant repercussions and to avoid confronting their own consciences.

The events that faced Krayer with a moral choice were unusual, from a historical perspective, but they were not unique. Fanaticism—political, religious, tribal, racial, intellectual, nationalistic—has periodically infected one or another part of the earth's population since civilization began. No country and no time is immune, and so the moral dilemma is an ever-recurring theme. During the agony of Vietnam, American academics could witness the same cautious neutrality on the part of most of their colleagues, at least until it became acceptable and popular to speak one's outrage. Apparently the simple ability to distinguish right from wrong and to act accordingly was incompatible with the scholarly temperament. "Not to decide is to decide," wrote the American theologian Harvey Cox. Most found it easiest "not to decide."

The surgeon Rudolf Nissen, writing of the German university faculties in 1933, has this to say:

> Another example of rare, almost isolated conduct amidst the crowd of opportunists was given by the Berlin Professor Extraordinarius, Otto

Krayer. His pupil, M. Reiter, has these wonderful words for this conduct: "The world is not particularly rich with people who prefer to jeopardize their career rather than sanction it with alien injustice. Nothing is more characteristic of Krayer's personality than his repeated refusal in 1933 to take over the chair in Düsseldorf, whose former holder, Philipp Ellinger, was driven from it on account of his race. The Professor Extraordinarius in Berlin, who was 34 at the time, did something that those in power felt was an open revolt and that many of his colleagues felt was at least inopportune and disturbing in the repercussions it had for them."[2]

Finally Nissen remarks: "It is unfortunate that such courageous and manly individual actions in the universities were not collected and made available to the public by officials who occupied themselves with the history of the Nazi period." He concludes by quoting Shakespeare (*The Winter's Tale,* act 1, scene 2) on the importance of publicly recognizing such actions: "One good deed, dying tongueless, slaughters a thousand waiting upon that."

Krayer's own laconic account of this landmark event in his life is found in an autobiographical sketch he wrote after his retirement for the *International Biographical Archives and Dictionary of Central European Emigrés,* 1933–45:

In the Spring of 1933, while engaged in collaborative studies with Prof. H. Rein in the Department of Physiology, University of Göttingen, I was asked by the Department of Education of the State of Prussia to take over the Chair of Pharmacology in the Medical Academy of Düsseldorf. The vacancy had been created by the dismissal of the Jewish incumbent Prof. Philipp Ellinger. Refusal to fill the vacancy because of my stated disagreement with the unjust policies of the government led to my immediate suspension by the Prussian Minister of Education from my academic positions. Moreover, I was forbidden to enter any university premises including University and State libraries. Returning from Göttingen to Berlin, where I could make use of private libraries, I was able to continue literary work in progress. I was especially anxious to complete and edit and to supervise the printing of Volume 2 of *P. Trendelenburg: Die Hormone,* a task

[2] Rudolf Nissen, *Helle Blätter—dunkle Blätter: Erinnerungen eines Chirurgen* (Stuttgart: Deutsche Verlags-Anstalt, 1969), pp. 140–44.

which had been entrusted to me by my teacher shortly before his death in 1931.

Later in 1933 Krayer's academic privileges at the University of Berlin were restored. However, he obtained a leave of absence and accepted an invitation to join the Department of Pharmacology at University College, London, with support from the Rockefeller Foundation, and on the last day of 1933 he departed Germany. There followed an intense and productive nine months of research in collaboration with E. B. Verney, who had been Starling's pupil. The substance of the investigations with Verney is recounted in a later section of this memoir. Krayer's former Berlin associate W. Feldberg, himself a recent refugee from the Nazis, was also in London. And dominating the scene was H. H. Dale, the foremost pharmacologist of the day.

In the autumn of 1934 Krayer was called to head the Department of Pharmacology at the American University of Beirut. His research and teaching accomplishments there are described later. Officially representing the American University of Beirut at the Tercentenary Celebration of Harvard University in 1936, he was asked to stay on for a few months as a lecturer in pharmacology at the Harvard Medical School. Then in 1937 an invitation was extended for Krayer to join the faculty as associate professor of pharmacology. He accepted and two years later became Reid Hunt's successor as head of the department, a position he held until his retirement in 1966.

A little-known event of his early days in Boston sheds further light on the idealism that was a strong motivating force in Krayer's life. The Nobel peace prize had just been awarded to the German writer and journalist Carl von Ossietzky, a pacifist of international renown, who had exposed the secret rearming of Germany and who had been (and was until his

death) incarcerated by the Nazi regime. Hitler's response to the award of the prize was a decree forbidding Germans to accept any Nobel prize in the future. At the regular meeting of the German Chemical Society on May 8, 1937, the president of the Society, Professor Stock, addressed himself to the honor bestowed upon von Ossietzky: "Every true German," he said, "must regard as a slap in the face this insulting abuse . . . an abuse dictated by political hatred. It is understandable that both the government and the people are indignant over this, and want nothing more to do with Nobel prizes . . . the crime of the Norwegian parliament's committee will be regretted deeply by Science."[3]

Krayer's immediate reaction was the following brief note to the society's office: "The remarks of President A. Stock concerning the award of the Nobel peace prize, which are printed on page 121 of the Proceedings of the German Chemical Society of 9 June 1937 oblige me to request that you strike my name from the list of members of the German Chemical Society."

Professor Stock, in reply, could only imagine that he had been misunderstood. "I was only reflecting the feelings of every German scientist," he wrote, "in being upset by such a conscious provocation . . . by the honoring of a person who—even before the time of Hitler!—had been branded a traitor; and in deploring that the scientific Nobel prizes had to suffer from this circumstance. . . . Perhaps you will be so kind as to write me a word of clarification."

Krayer's response will ring a familiar note for all who, as students or colleagues, came under his influence. It recalls the curious blend of careful reasoning and objective presentation of facts on the one hand, coupled with extraordinary

[3] A. Stock, "Opening Remark," *Berichte der Deutschen Chemischen Gesellschaft*, 70(1937):121.

emotional intensity on the other, that colored many of his formal lectures and informal discourses.

Dear Mr. President: I am happy to communicate to you the reason for my protest against your remarks. However, it is not my intention to enter into a discussion about the political expression "traitor". That this expression does not necessarily have a precise ethical value must be obvious to everyone who has experienced how easily the meaning can be changed by various political trends that appear especially strongly and clearly at times of upheaval in the structure of a State.

What made me write my letter of 3 September was the urge to express the view that not every German and—as I am convinced—not every German scientist shares your feelings of being upset by the award of the recent Nobel peace prize.

The reason for this conviction is what I have read over the last ten years of the writings of Carl von Ossietzky and have learned from other sources about him. I have had no occasion to meet this man personally. But whoever, over the past decade in Germany, has followed the course of his career in an unprejudiced way would—even if he were a political opponent—not be able to ignore the fact of the man's extraordinary personality.

Here is a man who, in a hard life full of work and an abundance of general human and political experience, has developed a world outlook and has deduced from it the principles of his life philosophy, who has made the profession of political writer his mission in life, and who is ready to dedicate to this profession not only all the strength of his spirit but also his whole personality. An unyielding character who, whenever the obligation of sincerity necessitates, openly uses his right of free speech to express his opinion. A man who is not motivated by the lust for power and fame but who is forced to speak by the persuasion of the rightness of his beliefs, and who fights unafraid for that persuasion with the force of his arguments. Carl von Ossietzky has proven the sincerity of his mind and his selflessness by again refusing (he had already been amnestied once) to evade responsibility for his convictions. To back up his words with deeds was a necessity of life for him although he must have known that he could not expect any justice from his political enemies.

The reason for such a judgment as you, Mr. President, have formulated, must be sought in an ethical evaluation of the man. I do not find

sufficient basis for your interpretation, and I am not of the opinion that the scientific Nobel prizes have lost any of their value or significance by the honoring of Carl von Ossietzky. It is to the credit of the Nobel organization that it honored the ethical qualities of this man; that is my conviction. What can promote peace between nations if not the deeds of such men, who are motivated by a pure and deep consciousness of their responsibility to a higher human order than is represented by the nation into which we [*sic!*] are born?

A final incident is noteworthy, again for the light it sheds on the ethical standards by which Krayer consistently guided all his actions. In 1965 the Academic Council of the Medical Academy of Düsseldorf voted to confer honorary membership on Krayer. Writing about this decision, the rector of the University explained as follows:

> They would like thereby to show their appreciation of the stand you took when, on grounds of conscience, you refused the call to the chair of pharmacology and toxicology in Düsseldorf in 1933, which would have been your first opportunity to be head of your own institute. At the same time the Academic Council wishes to acknowledge the fact that even after your emigration, and despite the unpleasantness you experienced in Düsseldorf, you nevertheless maintained and furthered your contacts with German science. Not the least, we would also like by our decision to acknowledge your scientific accomplishments, which relate to us in a special way through a traditional field of research at our Academy, namely, heart and circulation research.

Krayer's immediate response was to accept the honorary membership with pleasure. But as time passed, he evidently became increasingly uneasy. Somehow a mutually suitable date for the presentation ceremony in Düsseldorf could not be arranged. Finally, on January 26, 1966, Krayer sent what must have been a very difficult letter to write, as we can surmise from the three different preliminary handwritten drafts that are preserved, each full of deletions and alternative

wordings. Addressing the rector of the University of Düsseldorf, Krayer wrote:

> In the course of the correspondence with you concerning the time of my visit to Düsseldorf, I have thought more deeply about the honor you are planning for me. I have come to the conclusion that the right thing for me to do is not to accept the honorary membership of the Medical Academy of Düsseldorf.
>
> Despite my happiness at your first letter, which reached me during my trip to Japan, I had certain reservations from the beginning. It is now clear to me that the original ethical position I took in 1933 does not permit of any external reward. I must ask you, therefore, to nullify the decision of the Scientific Council of the Medical Academy. I regret that I took so long to express my convictions clearly.

Krayer closes with the hope that his decision will not cause bad feelings to mar his personal relationships with colleagues at Düsseldorf.

The reference, in the rector's original letter, to Krayer's maintaining and furthering contacts with German science will be cryptic to those unfamiliar with an episode that followed shortly on the close of World War II. With Central Europe literally in ashes, its universities and research institutes in ruins, and its people starving, the Unitarian Service Committee organized a medical mission to Czechoslovakia with Harvard cardiologist Paul Dudley White as director and Krayer as an active participant. During that trip Krayer became fully aware of the devastation of the German universities through personal visits with university colleagues. It must have been then that he formulated a plan for rendering special material and moral assistance to the German academic communities. On his return to Harvard, he founded, and served as secretary-treasurer of, a Committee to Help German University Scientists. By 1948 a medical mission to Germany had been organized by the Unitarian Service Committee, with Krayer as its chairman. This effort was supported

by the Department of State and by the U.S. occupation authorities. The visits to the universities of Frankfurt, Berlin, Göttingen, München, Tübingen, Freiburg, and Heidelberg brought a sense of concern and collegial friendship to supplement the material aid already being furnished by various groups in the United States.

## RESEARCH CONTRIBUTIONS

Krayer's first research, published in 1926, the same year he received his M.D. degree at Freiburg, concerned the pharmacologic properties of apocodeine, an opiate alkaloid closely related to apomorphine. In this work he first experienced the importance of employing only pure compounds in pharmacologic investigations—a recurrent theme in his later writings. Here he showed that apocodeine obtained from one manufacturer was pure and gave reliable and reproducible results, while impure mixtures behaved differently in important respects. Two investigations followed dealing with the pharmacologic and pharmacokinetic aspects of thyroid hormone action (1928a,b), no doubt inspired by the endocrinologic interests of his mentor Paul Trendelenburg. By 1929, however, he seems to have found his metier. In that year he published the first of two investigations into the cardiovascular toxicity of Neosalvarsan, an organic arsenical then in wide use for the treatment of syphilis. Thus was initiated a lifelong commitment to the study of the circulatory system.

Over a period of four decades, Krayer published seventy-six original research articles (not counting abstracts and textbook chapters), all but one in the field of cardiovascular physiology and pharmacology; the exception was a brief note concerning pumpkin seeds as a chemotherapy for tapeworm infestation, a byproduct of his brief stay at the American University of Beirut. Nearly all his research employed a single technique—the dog heart-lung preparation (HLP)—techni-

cally a very difficult setup of which he was the acknowledged world-class master.

From the purely statistical and descriptive aspects of Krayer's research career, there is much to be learned. By standards presently in vogue, one might judge a lifetime output of seventy-six original papers to be surprisingly scanty. Closer scrutiny, however, reveals several features decidedly no longer fashionable today. Of the total output, for example, one-third were sole-author papers; and Krayer was first author on another one-third. To those who knew him, these numbers merely express what we saw every day in the "heart-lung room"—a scientist with hands-on involvement in every phase of his research and a devotion to thoroughness that precluded the publication of incomplete or indecisive experimental results.

Nor did Krayer follow the traditional German procedure (now so common elsewhere, too) of making the department or institute head a pro forma coauthor of all papers by junior colleagues. Here numbers and names are instructive. In the last decade of his career at Harvard, for example, Krayer himself was first author on three papers and coauthor on ten others. In the same period, ninety-one additional investigations in the field of cardiovascular pharmacology were published by those working under his tutelage, and none of those carry his name. To Krayer, evidently, coauthorship implied direct responsibility for important aspects of the experimental work. He was always generous with suggestions, technical assistance, and criticism, but he would not put his own name to research unless he had been a direct participant. I consider it more remarkable now than I realized at the time that although at the beginning I was only a medical student engaged in part-time research in his department, it was taken as a matter of course that I would coauthor work for which Krayer had prime responsibility and would be sole author

when he had not been involved directly. This was for me a refreshing contrast to my one previous (and more typical) experience of publication, a short didactic clinical article I conceived and wrote without assistance, which my clinical instructor then submitted for publication with his own name added as first author!

Another interesting number is the mean length of Krayer's papers—11.2 pages—and the fact that one-quarter of them exceeded 14 pages. This, of course, was in the spirit of the times—and not only in the German literature so notorious for prolixity. If research was worth doing well, it was worth publishing well and fully. One's pride as a scientist simply ruled out the publication of incomplete or uncertain or fragmentary data. Modern biomedical science suffers from the "bit-by-bit" syndrome, wherein a staccato series of short papers report findings that may be raw, superficial, undigested, unconvincing, unexplored, and uninterpreted. Krayer's style, the very opposite, was to make each paper a complete *Arbeit,* every detail honed as nearly as possible to perfection. In an obituary on Otto Loewi (1962b), he wrote the following laudatory sentence, which is also an apt description of his own attitude: "He felt that any work worth publishing deserved as much care in the preparation of the manuscript as in the conduct of the experimental work."

Krayer held the belief that the aim of pharmacologic investigation is to elucidate mechanisms of drug action, that phenomenologic observations by themselves are only stepping stones to this ultimate goal. It follows automatically from this position that one's efforts have to be focused on a single problem and preferably on the perfection and use of a single methodology. The history of every field of science tells us that technique is the key to progress. Given the available knowledge base and technology, Krayer's adaptation of the Starling heart-lung preparation (HLP) to pharmacologic

investigations represented a major achievement. The HLP was a new and powerful tool, with which a lifetime of research on cardiovascular drugs could be carried out.

A fundamental problem in pharmacology is the multiplicity of the actions of most drugs. Even a drug that acted with absolute specificity on a single receptor would usually find that receptor in numerous organs throughout the body. And in reality most drugs have overlapping selectivities for more than a single type of receptor deployed in more than one organ system. Thus even the direct actions of a drug are often too complex to analyze in the whole animal. To this difficulty must be added the confounding effects of indirect (secondary) actions, such as physiologic reflexes or other adaptive responses to a primary drug action. This problem is especially serious for cardiovascular drugs since the heart and circulation are under continuous reflex regulation. Consider, for example, a compound that increases the heart rate. Does it do so by a direct agonistic effect on receptors mediating cardioacceleration at the pacemaker? By antagonist effect on receptors mediating cardiac slowing? By causing the local release of a cardioaccelerator neurotransmitter? By releasing a cardioaccelerator hormone from a distant tissue into the circulation? By stimulating chemoreceptors, leading to reflex decrease of vagal activity or increase of sympathetic tone? By causing a pharmacologic action remote from the heart (e.g., a decrease in blood pressure through relaxation of arteriolar tone) that leads to a reflex cardioacceleration?

In the HLP the heart and lungs remain in situ, but the entire output of the left ventricle (except for the coronary circulation) is routed through an external circuit. There the peripheral resistance is under the experimenter's control, and the height of the blood reservoir determines the pressure at which the right atrium fills. Oxygenation is provided in a quasi-normal manner by a respiration pump. The innervation can be left intact, or specific kinds of partial or

complete denervation can be carried out. Effects of drugs on the heart rate (chronotropic effects), force of contraction (inotropic effect), atrio-ventricular conduction (dromotropic effect), and other metrics can be studied. Thus the preparation offers a means to isolate sites and mechanisms of action of cardiovascular or cardiotoxic drugs free of multisite and reflex effects.

Krayer's first use of the HLP was during his Berlin period in the studies of Neosalvarsan toxicity (1929, 1930a). He discovered that the toxic agent was an oxidation product of the drug, and he showed that the effect was a direct one on the vascular beds of all the important organs. His succinct summary establishes the style that was to become his hallmark. Analyzing the evidence that the oxidation product causes a dose-related reduction of blood flow through the heart, lungs, kidneys, and liver, he concludes: "The increase in vascular resistance in these organs is to be attributed to changes in the vessels themselves. These changes are the cause of the far-reaching disturbances of hemodynamics, they are not the result of hemodynamic changes elsewhere."

Finding confusion among clinicians concerning the pharmacotherapy of heart failure, Krayer developed precise quantitative measures in the HLP, whereby cardioactive drugs could be characterized (1930b; 1931a,b,d; 1932b,c; 1933e). It was in his paper, "Versuche am insuffizienten Herzen" (1931d), that Krayer developed—extending the concepts laid down by his teacher P. Trendelenburg—a standard procedure for using the HLP to study drug effects on the failing heart. The competent heart increases its output in response to elevation of the venous reservoir without any significant increase in right atrial pressure—that is, the additional inflow leads responsively to an increased stroke volume. A large dose of a barbiturate reliably produced failure of a desired degree, which could be measured quantitatively as an impaired ability of the heart to respond this way. This

ability, after impairment by barbiturates, was enhanced by digitalis glycosides even in the denervated heart, that is, in the absence of any change in the heart rate. Later (1948b) this phenomenon was observed with other drugs known for their central depressant effects, and it occurred at concentrations that would have been in the lethal range for the whole animal.

The important advance in this paper was the demonstration of a method for determining quantitatively the limits of cardiac sufficiency in response to specific measured changes in right atrial pressure. Later a specific "competence index" was developed to express the heart's response numerically (1948b). This method allowed a clear distinction to be made between drugs that primarily affected heart rate and those (like digitalis) that truly improved the work capacity of the impaired cardiac muscle. The paper concludes: "A cardiac drug, in the most rigorous meaning of the term, must restore the ability of the failing heart to put out a greater volume per beat and thereby—and not simply by a rate increase—restore the limits of its sufficiency." Thus the study of the actions of cardioactive drugs could be pursued "under controlled conditions of heart failure."

Krayer's mastery of the HLP led to a very fruitful collaboration with W. Feldberg in the Department of Physiology at Berlin. Loewi's demonstration of chemical neurotransmission in 1921 had ushered in a new era for physiology and pharmacology. By the early 1930s, evidence indicated strongly that the *Vagus-Stoff* was acetylcholine, which could be identified in the leech muscle treated with the specific cholinesterase inhibitor physostigmine. The early experiments had been carried out with frogs. In the classical paper by Feldberg and Krayer (1933c), intact dogs and cats were used at the outset to show that an "acetylcholine-like substance" is released into the coronary circulation of mammals on electrical stimulation of the vagus. But here was also the perfect

opportunity to apply the HLP. The authors explain: "In order to make sure that as few extracardiac influences as possible modify the effect of stimulating the vagus, we considered it necessary also to demonstrate the *Vagus-Stoff* in the HLP." The same results were obtained in the HLP as in intact animals (Figure 1). Unless physostigmine was added both to the coronary circulation and to the bioassay preparation, and unless the vagus was stimulated, no "acetylcholine-like substance" was detectable. In a subsequent refinement of this experiment, Krayer (with Verney), soon after his emigration to London, showed that the vagus did not have to be stimulated artificially but could be stimulated reflexly by an induced increase in blood pressure (1934b). These ingenious experiments were carried out with an innervated HLP, the head (with no vascular connection to the heart) being perfused from a donor dog.

Krayer's interest in the veratrum alkaloids, which dominated his research interests from 1942 on, was stimulated, according to his own account (1962b), by his learning through a medical student's report that these substances were being used to lower blood pressure in eclampsia at the nearby Boston Lying-in Hospital. Crude extracts of the European *Veratrum album* (white false hellebore), the North American *Veratrum viride* (green false hellebore) (Figure 2), and the Central and South American *Veratrum sabadilla* (*Schoenocaulon officinale*) already enjoyed something of a reputation as beneficial in the management of heart disease. All parts of these plants—and also of the North American *Zygadenus* family—contain the cardioactive principles.

As long ago as 1818, Meissner and also Pelletier and Cavendou isolated veratrine, a potent alkaloidal mixture from sabadilla seeds. While still at Berlin, and recalling his earlier experience with apocodeine, Krayer had remarked on the futility of sophisticated pharmacologic studies with crude extracts. At that time he wrote: "Only when pure substances

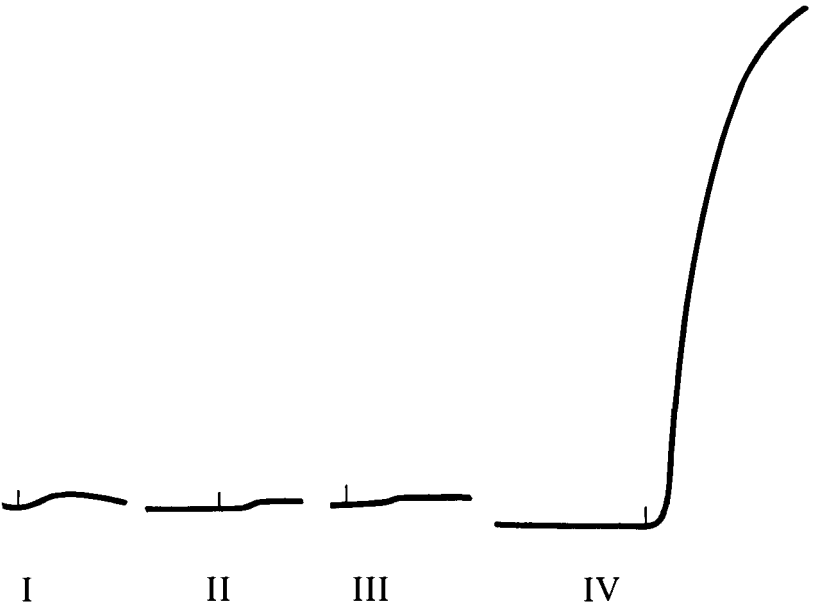


FIGURE 1 The first demonstration of acetylcholine release in a mammalian organism. Blood from the coronary sinus of a dog was tested on the eserinized leech muscle. Before injection of the cholinesterase inhibitor physostigmine, the blood had no effect on the leech muscle (I). Nor was there any effect of blood collected during electrical stimulation of the vagus (II), even though a transient cardiac arrest was produced. After the dog was injected with physostigmine and atropine, the blood was still without effect (III); but now vagal stimulation released an "acetylcholine-like substance" into the coronary blood (IV). [From Feldberg and Krayer, 1933b]. (Technical limitations made it necessary to reproduce this kymograph tracing and that in Figure 4 as black-on-white records rather than the original white-on-black.)

are available will it make sense to determine, by means of a thorough pharmacologic analysis, the conditions under which a favorable effect on the heart and an improvement of the circulation can be achieved" (1933d). Thus the initial experiments with a crude "veratrine" mixture (1942a) were immediately followed by studies on pure alkaloids. Krayer

FIGURE 2 *Veratrum viride*, popularly known as Indian pokeweed. This North American wild plant and related species that grow in Central and South America and Europe contain the cardioactive steroidal alkaloids in their roots, stems, and leaves.

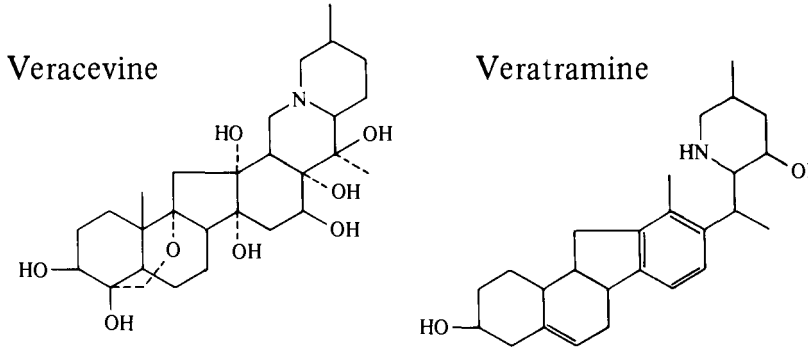


FIGURE 3 Typical structures of the two families of veratrum alkaloids. *Left:* Veracevine, the base of the ester alkaloid veratridine, which contains one mole of veratric acid (3,4-dimethoxybenzoic acid). Other ester alkaloids such as protoveratrine are mono-, di-, or tri-esters of various organic acids. *Right:* Veratramine, a typical secondary amine alkaloid, which occurs naturally as a glycoside with a single mole of glucose.

sought and received help from chemists, beginning in 1941 and continuing for the next twenty-five years. At the Department of Chemistry at Harvard, there were R. P. Linstead and D. Todd, later S. M. Kupchan, and then in his own department F. C. Uhle. Much help came also from W. A. Jacobs and L. Craig at the Rockefeller Institute and also from chemists at Eli Lilly and Company and Winthrop Chemical Company.

There are two major groups of veratrum alkaloids, the tertiary amine esters and the secondary amines (Figure 3), and their pharmacologic actions are entirely different. The special virtues of the HLP proved wonderfully suited to the investigation of these compounds, and Krayer studied them for the rest of his research career. Most of our present knowledge about the pharmacology of this group of naturally occurring cardioactive substances is due to that sustained effort by Krayer and his colleagues over the years.

The tertiary amine esters, such as protoveratrine A and veratridine, each contain a polycyclic polyhydroxylated amine (e.g., veracevine, as in Figure 3) and one or more organic acids. Much as with acetylcholine, the ester linkage proved to be essential to the full pharmacologic activity. The "veratrine effect" was well known in skeletal muscle—a repetitive discharge after a single stimulus, now recognized to be a consequence of the opening of sodium channels by the drug. The hypotensive effect is a reflex action caused by stimulation of chemoreceptors in the heart, lungs, and carotid sinus (the Bezold-Jarisch effect). The hypotension is accompanied by bradycardia, also of reflex origin, and is mediated by a vagal mechanism, as could be demonstrated by comparison of the innervated and denervated HLP (1943b,d; 1944b,c).

With the discovery of the reflex mechanism of action of the ester alkaloids, Krayer characteristically immersed himself in a scholarly investigation of the very early work of von Bezold and the later studies of Jarisch. Eventually he published a historical review with forty-nine citations, "The History of the Bezold-Jarisch Effect" (1961a), as a tribute to Professor Jarisch on the occasion of his seventieth birthday. One of the conclusions was that the name of this reflex, hitherto known as the Bezold effect, should more appropriately also bear the name of Jarisch.

Krayer's studies with the tertiary amine polyesters, especially protoveratrine A, led him to explore their therapeutic utility in human hypertension. With E. Meilman, a clinician at nearby Beth Israel Hospital, he carried out systematic studies on dosage, toxicity, and duration of action (1950b; 1952e; 1977). Protoveratrine A was chosen from among a number of candidate compounds for its favorable therapeutic ratio and long duration of action when given by the oral route. In contrast to veratridine, its action was more selective

for sensory nerves than for skeletal muscle. Also favorable was a positive inotropic action in the failing heart, as demonstrated by an increased work capacity in the HLP, later confirmed in patients. The positive inotropic action of veratridine or protoveratrine is of theoretical interest because of its similarity to the effect of the digitalis glycosides. Inhibition of the sodium pump (sodium-potassium ATPase) by the latter and opening of sodium channels by the former could both, through their different mechanisms, cause a net increase in sodium influx.

The basic pharmacology of the tertiary ester veratrum alkaloids is summarized in an exhaustive review by Krayer and Acheson (1946b). Protoveratrine A had some usefulness for a time in the treatment of malignant hypertension, hypertensive encephalopathy, and eclampsia (1949h, 1958a). Since it effectively lowered the "set point" for reflex control of the blood pressure without disturbing the adaptive reflexes themselves, it did not (for example) cause postural hypotension such as is common with the autonomic ganglionic blocking agents. Unfortunately, nausea and vomiting were common side effects (also from stimulation of vagal afferents), and in time a whole armamentarium of more effective antihypertensive drugs was developed. Thus protoveratrine A was eventually superseded, but it undoubtedly played a seminal role by pointing the way to a practical pharmacotherapy of hypertension.

The secondary amine alkaloids and their glycosides proved to have an entirely different pharmacology from the tertiary amine esters despite the close similarity of chemical structure. These compounds, of which veratramine (Figure 3) is the best studied, are also hypotensive in their action, but their most interesting effect proved to be a cardiodeceleration by a direct effect on the cardiac pacemaker (1949d,f,g). There were two main lines of evidence. First, the effect was

not blocked by atropine, which abolishes the action of acetylcholine released by the vagus. Second, in the denervated HLP infused continuously with epinephrine, the steady-state marked increase in heart rate is promptly abolished by small doses of veratramine. At the same time the positive inotropic action of epinephrine remains unchanged. Thus this experiment sharply separates the cellular mechanisms that mediate the chronotropic and inotropic effects of the catecholamines (Figure 4). The novelty lay in the fact that although antagonists to the pressor action of epinephrine had been discovered, no antagonist to the cardioaccelerator effect was known.

Most of the thirty-seven papers in the series entitled "Studies on Veratrum Alkaloids" dealt with these secondary amines and their glycosides. Related steroid alkaloids with similar pharmacologic effect were found among the compounds isolated from plants of the *Zygadenus* and *Solanum* families. The aglycones and glycosides were found to be equipotent. Investigations of the structure–activity relationships, which included a group of novel steroids synthesized from pregnenolone by F. C. Uhle in Krayer's department, revealed that high potency required the N atom to be in a piperidine ring.

The selectivity of veratramine and its congeners for the pacemaker tissue intrigued Krayer. Not only did veratramine lack the positive inotropic actions of epinephrine, it also lacked all the other characteristic cardiovascular effects of the catecholamines. It did not constrict the peripheral arterioles and therefore lacked pressor action. It did not dilate the coronary vessels. It did not share the depressant effects of epinephrine upon the functional refractory period and A-V propagation time within the heart. Krayer wrote: "When a group of substances exhibits a high degree of selectivity of action, it should attract the investigative curiosity of the phar-

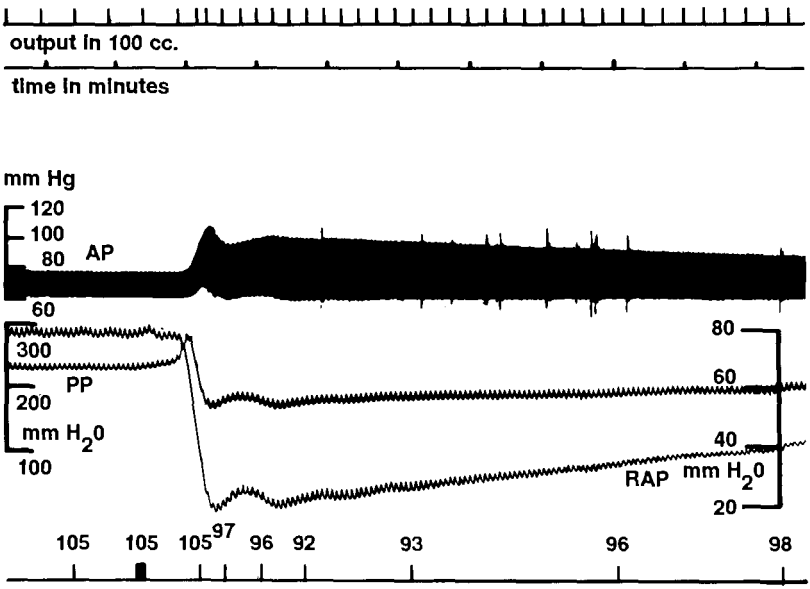


FIGURE 4 Dissociation, by means of veratramine, of the chronotropic and inotropic actions of epinephrine. The record is from a dog HLP in failure, treated with veratramine during the previous two hours. Epinephrine (10 micrograms) was administered at the broad marker signal on the bottom line. Within a minute, epinephrine increases the cardiac output (top line), thus lowering the elevated right atrial pressure and pulmonary pressure; it also increases the systolic arterial pressure—all without any increase of heart rate. *Symbols:* AP, arterial pressure; PP (lower curve on left, middle curve on right), pulmonary pressure; RAP (middle curve on left, lower curve on right), right atrial pressure; bottom horizontal row of figures, heart rate per minute. [From Krayer, 1949d]. (See parenthetic note under Figure 1 legend.)

macologist. The search for selective activity and the analysis of its nature is the central theme of his scientific pursuit" (1952d).

As Krayer learned later (1958d), the direct action of the secondary amine alkaloids on the pacemaker was not a blockade (at the receptor level) of the accelerator action of the catecholamines. Thus, veratramine was not a true forerun-

ner of the beta-adrenergic receptor blocking agents, which have proved to be so useful therapeutically. Krayer's work, however, was the first demonstration that a cardioselective antagonism of a noradrenergic physiological effect at the sino-atrial node was possible.

Often, as plant alkaloids of various families became available in pure form, Krayer would test their effects in the HLP. Thus it was that in 1955 he began to examine the action of reserpine, a pure alkaloid from *Rauwolfia.* The *Rauwolfia* alkaloids had long been used in India for their tranquilizing effects, and the early 1950s had seen intensive interest in their therapeutic potential in Europe and the United States. Reserpine had been introduced into psychiatric practice as a tranquilizer and also for its antihypertensive effect. Because reserpine was regarded as primarily a psychopharmacologic agent, those interested in its mechanism of action naturally turned to the brain; even the hypotensive effect was presumed to be centrally mediated. It had already been shown, first in Brodie's and then in Marthe Vogt's laboratory that reserpine depletes the brain of its serotonin stores, and this same approach was being extended to brain catecholamines in several laboratories.

The immediate stimulus for Krayer's interest was a letter in the *New England Journal of Medicine* reporting heart failure in patients treated with reserpine. Krayer seized the opportunity to exploit the unique value of the HLP for distinguishing direct peripheral actions of drugs from those requiring intact innervation, and he was soon able to sort out the components of reserpine's actions. The alkaloid produced an immediate cardioacceleration that was similar in all respects to that of an infusion of norepinephrine. Matti Paasonen, a visiting scientist from Finland, measured tissue and blood catecholamine levels and found that the norepinephrine content of the heart fell sharply—that is, reserpine depleted the cardiac stores. In the HLP from reserpine-pretreated dogs,

reserpine failed to produce the characteristic cardioacceleration. Moreover, serotonin infusions had no effect on the heart rate, showing that serotonin release (which also occurs) does not participate in the cardioaccelerator action. An additional finding of interest, revealing an independent effect of reserpine, was that in the HLP under the rate-increasing effect of a catecholamine infusion, reserpine reduced the heart rate in an atropine-resistant manner reminiscent of veratramine. All these effects occurred also in the denervated HLP, permitting the conclusion that ". . . reserpine exerts an action upon the heart in the absence of connections with the central nervous system" (1958b). Curiously (although it was not realized until later), the release of catecholamines in amounts sufficient to produce effects of their own was a peculiar property of the HLP, not evident in most organs or in whole animals. These important studies were published originally in 1957 in three abstracts—in *Federation Proceedings* (1957a), *Acta Physiologica Scandinavica* (1957b), and the *Journal of Physiology* (1957c).

In summary, Krayer had shown that reserpine depletes biogenic amine transmitters from peripheral as well central stores by a direct action. Thus the reserpine effect was a general phenomenon, not limited to the central nervous system, and this was pointed out explicitly in one of the 1957 abstracts. As so often happens, however, the same discovery was made almost simultaneously in several laboratories. Carlsson's group in Sweden was studying the depletion of catecholamines in peripheral as well as central tissues. A short paper from this group,[4] which was submitted for publication October 20, 1956, reported on the depletion of catecholamines from rabbit heart by reserpine. They also showed that

[4] A. Bertler, A. Carlsson, and E. Rosengren, "Release by Reserpine of Catechol Amines from Rabbits Hearts," *Naturwissenschaften,* 43(1956):521.

reserpine-treated adrenalectomized cats given carbachol to stimulate sympathetic ganglia and atropine to block the muscarinic actions of carbachol had no blood pressure rise, as they would normally have done as a result of norepinephrine release at the sympathetic nerve terminals in arteriolar walls. Moreover, electrical stimulation of the splanchnic nerves was without its usual hypertensive effect in these animals.

On March 22, 1957, Brodie et al. (National Institutes of Health) submitted a paper under the title "Possible Interrelationship Between Release of Brain Norepinephrine and Serotonin by Reserpine."[5] The paper also included a report of the depletion of norepinephrine from rabbit heart even after high cervical section of the spinal cord, showing that the depleting action of reserpine was direct and not centrally mediated.

The British pharmacologist J. H. Burn (Oxford) visited Krayer in 1957. In a letter dated May 7 of that year, expressing thanks for hospitality, Burn wrote: ". . . I enjoyed seeing the results with reserpine in the heart-lung preparation." More than a year later, on June 3, 1958, Burn and Rand submitted for publication "The Action of Sympathomimetic Amines in Animals Treated with Reserpine."[6] This major contribution established very thoroughly that reserpine depletes the stores of norepinephrine in arterial walls. In addition, several bioassay preparations from reserpine-treated animals were used to demonstrate that some sympathomimetic amines (e.g., tyramine and other noncatechol phenylethylamine derivatives) only act when the tissue catecholamine stores are intact, and therefore presumably owe their

[5] B. B. Brodie, J. S. Olin, R. G. Kuntzman, et al., "Possible Interrelationship Between Release of Brain Norepinephrine and Serotonin by Reserpine," *Science*, 125(1957):1293–94.

[6] J. H. Burn and M. J. Rand, "The Action of Sympathomimetic Amines in Animals Treated with Reserpine," *Journal of Physiology (London)*, 144(1958):314–36.

own actions to the release of catecholamines. In addition, it was reported that tissues from reserpine-treated animals were supersensitive to catecholamines and that both the insensitivity to tyramine and the supersensitivity to catecholamines could be reversed by an infusion of norepinephrine that repletes the stores. Further significant conclusions were that a continuous slow release of norepinephrine from arteriolar stores probably plays a role in maintaining the normal vascular tone and also that circulating catecholamines from the adrenal gland probably participate in maintaining the stores at their proper level. This paper had an immediate and lasting impact in physiologic and pharmacologic circles; it is still regarded as a landmark contribution.

The full-length 1958 papers from Krayer's group (1958b,d,e,f) had not appeared in print when the manuscript by Burn and Rand was submitted for publication. Curiously, however, none of Krayer's three 1957 abstracts is cited, nor is any "personal communication" acknowledged. We know from his intimate associates that Krayer felt miffed; he may even have thought that Burn made improper use of what was learned during the May 1957 visit. A letter from Burn to Krayer dated October 11, 1958, is interesting in this respect. Edith Bülbring, one of Burn's colleagues at Oxford and a longtime friend of Krayer (they were colleagues in the Berlin days), had just returned from a visit to Boston. Burn writes: "A remark of Edith's since her return prompts me to write to you about my interest in reserpine, and how it began." There follows a detailed historical account and then the following passage: "I know that you showed me the action of reserpine on the rate of the heart-lung preparation in 1957, but it passed from my mind and played no part in my thoughts. I had forgotten what you showed me until I read your papers a month or two ago."

In one of the papers on reserpine that was published

from Krayer's laboratory in 1958, Innes and Krayer (1958d) compared the negative chronotropic effects of reserpine and veratramine. Using the HLP from reserpine-treated catecholamine-depleted dogs, they showed that the action of veratramine was unchanged and therefore that it did not act by antagonizing sympathomimetic amines. Until then such an adrenergic blocking mechanism could not be ruled out. It had earlier been shown that when the heart rate was elevated to a high steady-state level by an infusion of epinephrine or norepinephrine, veratramine lowered it dramatically. In the absence of added catecholamines, it also reduced the heart rate, but the normal heart rate might have been under the tonic accelerator action of a slow release of endogenous norepinephrine. Only by substantially eliminating the catecholamine stores could the direct depressant effect of veratramine on the atrial pacemaker be proved.

In another paper Innes, Krayer, and Waud (1958e) examined ten *Rauwolfia* alkaloids and showed that, whereas they all displayed a direct depressant effect on both the heart rate and atrio-ventricular transmission, only half of them were catecholamine depleters. Waud, Kottegoda, and Krayer (1958f) studied dosage and time-course details of the depleting effect of reserpine. Their method was to pretreat the dog with various doses of reserpine 24 hours prior to a challenge dose on the HLP or, alternatively, to pretreat with a standard dose at different times prior to the challenge. In this clever method the attenuation of the heart-rate increase caused by the challenge dose serves as a measure of the degree of catecholamine depletion by reserpine. They found a very slow onset of action of reserpine, peaking at 24 to 72 hours, and a good correlation with norepinephrine content (determined by bioassay on the cat blood pressure) throughout the time course. The threshold single dose was found to be a remarkably low 30 micrograms per kilogram.

In 1960 Waud and Krayer published a study that is a model of the application of sophisticated statistical methodology to a complex pharmacologic problem—a so-called "split-split-plot design." Epinephrine was compared with norepinephrine and shown to be equipotent. The HLP was found to become progressively less sensitive (as an experiment continued) to the cardiovascular effects of both catecholamines. Finally, reserpine pretreatment did not influence the effects of norepinephrine or epinephrine on the heart rate. This last conclusion was contrary to the findings of Burn and Rand. Burn, in a letter to Krayer, took issue, asserting that the method of catecholamine infusion could not have detected the reserpine-induced supersensitivity inasmuch as the infusion itself would quickly replete the stores. Waud and Krayer themselves acknowledge in their discussion: "The use of single doses might also contribute to the discrepancy." Inasmuch as their paper cites Burn and Rand, who showed that an infusion of norepinephrine abolishes the supersensitivity, it is surprising that Waud and Krayer did not compare single doses with infusions in their own experiments.

Papers in 1962 (Krayer, Alper, and Paasonen), 1966 (Krayer, Mosimann, and Silver), and 1972 (Krayer, Weiner, and Mosimann) completed the studies on catecholamine depletion. Guanidine derivatives had been found to share this action with reserpine, guanethidine having been studied principally in this respect. Krayer compared guanethidine with reserpine in the HLP; here he found that the catecholamine-depleted preparation was sensitized to both the chronotropic and inotropic effects of norepinephrine. Further studies employed a very simple compound, methylguanidine, which is 250 times less potent than guanethidine but has the same pharmacologic effects. By now, fluorimetric methods of catecholamine assay had been introduced, and these made possible precise, direct measurements in the coronary sinus

blood. Methylguanidine always produced a higher level of norepinephrine in coronary sinus blood than in arterial blood that had passed through the pulmonary circulation, showing that the elevated norepinephrine was indeed derived primarily from cardiac stores.

Krayer's studies on reserpine never had the historical scientific impact they deserved. The reasons are evident in retrospect. His focus on the HLP tended to limit his "audience." Moreover, his steadfast refusal to draw a conclusion that went beyond his own data meant that the broad significance of the reserpine findings did not "leap off the page." It is true that the field quickly became competitive, whereas Krayer's discovery of catecholamine depletion was probably unique in 1955. Painstaking thoroughness about every aspect of experimentation and the preparation of manuscripts accounted for the passage of two years until the first brief meeting abstracts appeared, and three years until the first full-length papers were published. More than sixty HLP preparations were used for Krayer and Fuentes (1958b), about thirty-seven for Paasonen and Krayer (1958c), twenty-five for Innes and Krayer (1958d), and forty-four for Waud, Kottegoda, and Krayer (1958f).

Finally, it was not Krayer's style to promote his own work by aggressive public pronouncements, nor to engage in "priority battles." Certainly, he would never have voiced his concern in public over matters of scientific priority, and he disdained secrecy in the laboratory, always welcoming visitors and freely discussing work in progress with them. Not only the intensely competitive environment that developed around reserpine but also the passionate disputes over the relative importance of norepinephrine depletion and serotonin depletion disgusted him, and probably accounted for his withdrawal from further research on the reserpine problem. In retrospect there is no doubt that his studies, limited

as they were, nevertheless represented an important contribution to the biochemical pharmacology of the catecholamines, with implications for physiology and pharmacology that reached far beyond the cardiovascular system.

Krayer's mastery of the HLP as an experimental tool placed him virtually in a class by himself. His department, at the peak of its activity from the late 1950s until his retirement in 1966, was certainly one of the world's leading centers for the training of cardiovascular physiologists and pharmacologists of the traditional kind. Yet it was the end of an era. Young physiologists and pharmacologists were turning increasingly to the methods of biophysics, biochemistry, and molecular biology to solve fundamental questions about physiologic mechanisms and their alteration by drugs. Krayer has to be seen, in historical context, as one of the last and one of the greatest in the long tradition of physiologic pharmacologists.

He was not only a master of the HLP, he was also a master of kymography. In an obituary memoir, P. B. Dews, long a member of Krayer's department, wrote: "Krayer brought kymography to its highest level as an art." We who experienced the transition from crude mechanical recording devices to electronic ones (polygraphs) can perhaps understand better than our younger colleagues the significance of kymography practiced as an art. To produce experimental records of the quality evident already in Krayer's Berlin publications of 1929–1933 implied an attention to detail affecting all aspects of an experiment. Thus kymography was a kind of window on the experimenter's methodology through which one could form some judgment of the overall quality of the work. The published experimental records let us appreciate the fastidious attention to detail that was his credo. Close inspection of any figure from his publications (e.g., Figure 4) must elicit admiration even from users of modern electronic recording

devices. He had a stubborn pride in his ability to tame a difficult preparation and make it serve sophisticated purposes. He enjoyed the directness and truthfulness of the kymograph, and he was ever suspicious of the "black boxes" between input and output in modern experimental procedures. Above all, he took pleasure in squeezing the maximum of quantitative data out of so gross and intrinsically crude a bioassay system (cf. Waud and Krayer, 1960).

His perfectionism about scientific publication included a strong insistence on the correct use of words. His philosophy about this is expressed, in part, in a publication summarizing many of his studies on drugs affecting the heart rate (1963a). He alludes to Engelmann, a turn-of-the-century physiologist who coined the term "chronotropic," and he discusses a widespread confusion between direct and indirect chronotropic effects. He writes as follows:

> The creation of new words for new or old concepts is a continuous process in the biological—as in other—sciences. Men like T. W. Engelmann, and in our own time for example, H. H. Dale, who combine this creative ability with a deep biological knowledge and clarity of thought, are rare. As I have sought to demonstrate, the progress of science makes old concepts inadequate. It is therefore not surprising that scientific vocabulary should lose its precision through misuse of old terms and through poor choice of either old or new terms for new concepts. The time is ripe now for a systematic attempt, in physiology and pharmacology, to preserve the significance and beauty of our scientific language. The academic scientist has a dual obligation–not only to make advances in our understanding but also to create the appropriate new language to describe those advances.

## PERSONAL HISTORY

Otto (Hermann) Krayer was born October 22, 1899, the second child and first son of Hermann and Frieda Berta (Wolfsperger) Krayer, in the village of Köndringen (Baden), Germany. The Krayers, like most of the villagers, were churchgoing Protestants. They were relatively well off, at

least by the standards of this farming community of about one thousand inhabitants. They ran an inn (the Zum Rebstock) and a butcher shop, and they farmed. The father served as treasurer of the village. Before and after school there were chores for the children to do in the fields, vineyards, barnyard, and home. The boy developed a feeling of closeness to the land and to nature—a feeling he often expressed in later years. And though he lived most of his life in Boston and then in Tucson, Krayer always considered the little village at the edge of the Black Forest as home. The local dialect—Alemannic, virtually incomprehensible outside southern Germany and Switzerland—rolled easily off his tongue, and tales are told of his experimental dogs being castigated in that language at moments of exasperation. His attachment to Köndringen was lifelong. His mother lived to a very old age, and Krayer visited her in the old homestead on many occasions. He often said that among all the honors accorded him, the one that meant most was that of honorary citizenship of Köndringen, bestowed in 1957.

Young Krayer's intellectual gifts attracted the attention of the local schoolmaster and of the minister, who persuaded the parents to continue the boy's education. Thus he attended the six-year middle school in the nearby town of Emmendingen. This was followed by another three years of schooling in order to qualify for university matriculation, and he began these in the nearby city of Freiburg. However, World War I was in progress, and his education was interrupted when he turned eighteen: He was conscripted on June 19, 1917, and after half a year of infantry training was sent to the Western Front. A combat wound shortly before the armistice sent him to hospital and then, while still convalescing, he completed the educational requirements for university entrance. Finally, in the autumn of 1919, he enrolled as a medical student at the University of Freiburg.

The course that mainly captured Krayer's interest at the outset was gross anatomy. He discovered real joy in the use of manual skills for dissection—no doubt a foretaste of the pleasure he would experience in setting up hundreds of heart-lung preparations during his career. Years later he wrote about these early dissection experiences: "The beauty of the forms and the relation between form and function became a source of great satisfaction."

In the autumn of 1920, following the German student tradition of moving from university to university, Krayer transferred to the University of München. Here the professor of histology, Siegfried Mollier, made a lasting impression. "Every one of his lectures," Krayer recalled, "was a feast for the mind and the eye. His joy, uttered in a word of approval when he recognized in the drawing of a microscopic structure that the student had caught its beauty, made the course in microscopic anatomy a memorable, intellectually and spiritually enriching experience."

For his clinical studies Krayer returned, in 1922, to Freiburg. His love of the outdoors took him on long walks through the countryside, in the foothills of the Black Forest and along the little river Elz. Here was rooted his lifelong love of botany; he always made a point of knowing all the native plants and flowers of whatever region he was living in. In the winters he was fond of skiing, and he was expert enough to win a student ski competition. The prize, donated by the pharmacologist Walther Straub, is said to have been a single U.S. dollar—a princely sum in those days of rampant inflation in Germany. And here on the ski slopes near Freiburg he enjoyed the companionship of a classmate, Erna Ruth Philipp, who was (much later) to become his wife.

He found the didactic courses in medicine and surgery uninspiring, the more so as there was hardly any contact with patients. Seeking more intellectual stimulation, he undertook

his first experimental research at this time—a project in the comparative morphology of amphibian kidneys, under the direction of Wilhelm von Möllendorf. Krayer would collect the specimens himself in the field—often near his native village—and make microscopic measurements on glomeruli and proximal tubules after vital staining with trypan blue.

Enthusiasm for research led Krayer next to pharmacology professor Paul Trendelenburg, whose personality and lectures had made a strong impact on him. After completing his formal course-work and passing the university and state examinations at the end of 1924, Krayer spent the first half of 1925 full time in Trendelenburg's department. In the second half of 1925 he fulfilled internship requirements in internal medicine. Finally, in 1926, he received the M.D. degree for his dissertation research on apocodeine, and he formally began his career in pharmacology as *Assistent* under Trendelenburg.

Krayer's deep commitment to teaching must have had its roots in this Freiburg period. His task was to prepare the lecture demonstrations. These were the students' only opportunities to observe the effects of drugs on animals; there were no facilities for routine laboratory teaching of medical students. It is interesting, in the light of Krayer's later strong belief in the importance of practical laboratory work in pharmacology for medical students, that in 1927 he embarked on what was then a radical innovation—a small, elective experimental laboratory course. Seven years later, in a letter requesting a leave of absence to study laboratory teaching, American style, at the American University of Beirut, he wrote as follows: "This form of instruction has outstanding advantages, provided it is carried out with the necessary earnestness and the number of students is not too great . . . as compared with a method that is based almost entirely on the

textbook and spoken word, i.e., on knowledge divorced from experience."

Trendelenburg's interests lay in endocrinology, and at that time he was completing the first volume of a major treatise, *Die Hormone. Ihre Physiologie und Pharmakologie.* Krayer naturally began investigations in that field. He undertook a study of the relation between thyroid function and the autonomic nervous system and published some results (1928a). However, the aspect of endocrinology that dealt with the adrenal medullary hormone epinephrine turned Krayer's interests to the circulatory system. Soon he began to assemble equipment for the heart-lung preparation, which had been introduced by E. H. Starling. Attendance at the International Physiology Congress at Stockholm in 1926 gave Krayer the opportunity to meet some of the leading cardiovascular physiologists and pharmacologists of the day—Starling himself, J. H. Burn, and G. Liljestrand. Among the many visitors to the Freiburg department was H. B. van Dyke, who later became professor of pharmacology at Peiping Union Medical College and then at Columbia University, and who became a lifelong friend.

When Trendelenburg assumed the chair of pharmacology at Berlin in 1927, Krayer went with him. There he advanced rapidly through the academic ranks, from *Assistent* to *Oberassistent* to *Privatdozent.* He had by now turned his research interests fully to the circulatory system; the two mandatory lectures to qualify for the appointment as *Privatdozent* were on coronary blood flow (for the faculty) and on the analysis of the circulatory actions of drugs (for the public).

Trendelenburg became seriously ill in 1930, and Krayer had to assume full academic responsibility for the department. Then, with his chief's death in 1931, Krayer was made acting head; the following year—at the age of thirty-two—he was promoted to Professor Extraordinarius of Pharma-

cology and Toxicology. Now research had to be put aside while he dealt with the heavy teaching load: the required course in pharmacotherapy, an elective laboratory course, and special elective courses on cardiovascular pharmacology and industrial toxicology. The system of oral examinations for all medical students required his personal participation in more than 500 of these per year. He was also required to assist the courts with forensic toxicologic analyses and even ad hoc experimental studies. In addition, it was necessary to supervise the planning for a new building for the Department of Pharmacology.

Trendelenburg had left two literary legacies—his uncompleted second volume on the hormones and a textbook on the principles of therapeutics, the second edition of which had appeared in 1929. Krayer inherited both. The third edition of the textbook was brought to publication in 1931, but the more demanding task of completing the second volume of *Die Hormone* had to be deferred until the spring of 1932, when W. Heubner was appointed head of the department. Research could then also be resumed, and it was at this time that the important collaborative study with W. Feldberg was initiated. A leave of absence in April 1933 allowed Krayer to join H. Rein, the new professor of physiology at Göttingen, to pursue collaborative experiments with the HLP. But these plans were abruptly terminated in June by the events described at the opening of this memoir.

Returning to Berlin, Krayer found ways (despite the ban on his use of state libraries) to obtain the necessary books and journals needed to complete *Die Hormone.* One of those who assisted him at this difficult time was Dr. Erna Ruth Philipp, who had been a fellow medical student at Freiburg and eventually was to become Krayer's wife. In August Krayer received Verney's invitation to University College and in November an offer from van Dyke at Peiping. The Nazi authorities rein-

stated him in September, whereupon he requested and was granted a one-year leave of absence for study abroad. On December 31, 1933, with a fellowship from the Rockefeller Foundation, he left Berlin for London.

In Verney's laboratory Krayer plunged into research with the dog heart-lung-kidney preparation as his tool. The aim was to obtain quantitative information about the effects of antidiuretic hormone on kidney function. Using intact dogs equipped with indwelling ureteral catheters, he developed a method of standardizing the hormone. But Krayer's most significant work in the first half of 1934 was the demonstration with Verney (1934b, 1935b) that a physiologic indirect stimulus—a vagal reflex—would release acetylcholine into the coronary circulation. This added considerably to the force of the earlier proof (with Feldberg) that direct stimulation of the vagus released acetylcholine.

Within a few months Krayer was approached about the possibility of assuming direction of the Department of Pharmacology at the American University of Beirut. At the same time he was a leading candidate for the chair of pharmacology at Zurich. By the end of the summer he had accepted the Beirut position, technically a visiting professorship, and here his former associate in Freiburg and Berlin, Dr. Erna Ruth Philipp, joined him as his literary assistant. Because the class was small and newly built facilities were available, he was able to realize his dream of teaching pharmacology primarily as a laboratory course. Among the students who were attracted to his department for research experiences, at least two were inspired to pursue careers in pharmacology. These were Alfred Farah, who later joined Krayer at Harvard and then became department head at Syracuse; and George Fawaz, who eventually became professor of pharmacology and head of the department at Beirut. Glimpses into Krayer's personal life in Beirut are afforded by Fawaz, who describes a

vigorous outdoor regimen of hiking and climbing and trips on horse-back—experiences that led to a deep attachment to the scenery of the region. Mount Sannin near Beirut especially captured Krayer's imagination, as did the alpine beauty of Mount Lebanon and its famous cedars. And in winter there was skiing. "Krayer on skis," according to Fawaz, "was an entirely different person: jolly, and uninhibited as a child." Explaining why Krayer gained the respect and love of all members of the University community, Fawaz writes:

> The explanation is simple: he was considerate and modest and demanded very little for himself and his own comfort. His ego never played a role in his decisions. His main concern was his work, which he performed conscientiously; he then sought to serve his students and friends. . . . However, his natural docility abandoned him when he was lecturing or demonstrating an experiment. Then he was transformed into an evangelist, full of zeal.

Although he carried on some research during the three-year stay in Beirut, including a study on pumpkin seeds as anthelmintics (1937), his chief preoccupation was teaching and revising the fourth edition of the Trendelenburg textbook of pharmacotherapy (1938). His sojourn in Lebanon left deep and lasting impressions of the natural beauty of that semiarid region remarkable for its mixture of populations and cultures. "The country is, to my taste, of an exceptional beauty," he wrote to his successor J. O. Pinkston. The circumstances of Krayer's seemingly impulsive decision, thirty-five years later, to spend the latter part of his life in Tucson—much to the surprise of former students and associates who had tried to attract him, after his retirement, to their own geographic areas—suggest that the desert beauty, the stark mountains, the climate with its rainy and dry seasons, and the ethnic diversity of Arizona evoked again all his strong positive feelings about the Beirut experience.

In 1936 Krayer was sent to Harvard's tercentenary celebrations as the official representative of the American University. Whether this was part of a grand design to move him to Harvard, or whether it was just a fortunate turn of events, is unclear. We do know that Krayer had made the acquaintance of Walter B. Cannon at the International Physiology Congress in the summer of 1935 in Moscow. Cannon was professor of physiology at Harvard Medical School and one of the world's foremost physiologists. And Cannon was the moving spirit in arranging a three-month appointment for Krayer as a lecturer in pharmacology for September, October, and November 1936. In 1937, shortly after his return to Beirut, the invitation was proffered to become, in effect, the successor to Reid Hunt, who had retired a year earlier as head of the Department of Pharmacology. We shall probably never know the details of the internal academic politics behind this curiously ambivalent appointment as associate professor without tenure and acting head of the department. Perhaps it was only shrewd Yankee trading practice to offer as little as possible; this is the interpretation put forward by Peter Dews in his obituary article. I think it was probably more than that, in view of Krayer's difficulties with the medical school administration over the next fourteen years. We can only speculate.

Those were the days—now happily gone—when ethnic and national and cultural diversity were counted as liabilities rather than as assets to an institution. The faculty and student body of Harvard Medical School were overwhelmingly white Anglo-Saxon Protestant males (indeed, women were excluded as a matter of explicit formal policy). And here was this rather intense foreigner, not exactly fitting the "old Harvard" mold. Acceptance was probably made no easier by Krayer's European mannerisms, an excessive formality (by American standards), and a stern—even moody—tempera-

ment. No easygoing, back-slapping, "old boy" camaraderie here; one could not imagine him cheering at a football game, playing a rubber of bridge or a round of golf, telling (or laughing at) a dirty joke. With close friends, however, the stern demeanor vanished, and he engaged readily in relaxed and good-natured banter or even teasing. His absolute rectitude must have repelled some, even while it attracted others. We know, furthermore, that prominent American pharmacologists communicated to the Harvard administration their displeasure that no qualified American had been found to fill the prestigious post.

When Krayer arrived, the department was a shambles. The only other faculty member was occupied nearly full time with administrative chores in the dean's office, equipment and facilities were primitive, and the school provided only a miniscule budget. Krayer became increasingly disillusioned with the situation and especially with the lack of support from the medical school administration. Six months after his arrival he was offered the chair of pharmacology at Peiping, which had been vacated when van Dyke moved to Columbia. Krayer was strongly inclined to accept, and on June 23, 1938, he actually informed Dean C. S. Burwell that he planned to accept the Peiping offer effective September 1939. What happened next may well be unique in the history of Harvard Medical School. In January 1939 the entire medical school class of 1941, who were in the midst of their pharmacology course, and many of the class of 1940, who had been taught pharmacology the previous year, petitioned Krayer to stay and delivered a copy of their petition to the dean. The document, with 152 signatures appended, reads as follows:

> We, the undersigned, have heard with regret of your plans to leave the Harvard Medical School. Students naturally form opinions of their teachers. As your students we wish to express our admiration for your teaching, our gratitude for all your efforts on our behalf, and our hope that, should

future developments make it possible, you might stay here to give coming classes something of what you have given us.

Forty-five years later, this episode was recalled vividly by one of its participants, Curtis Prout, as follows: "All of us signed it with great enthusiasm. . . . The morning following this action, when we had delivered one copy to Dean Burwell and put the other under his (i.e., Krayer's) door in Vanderbilt Hall, he gave his lecture as usual; it was technical, almost dry but precise and a gem. At the conclusion of the lecture, he started to walk out of the amphitheatre but just before he got to the door, he stopped, turned around, looked up, and he said, 'I have received your petition. Thank you very much.' and quickly made his exit. We gave him a round of applause." For all who knew and admired Krayer, this description of his restrained and dignified reaction to so extraordinary an event will ring absolutely true. At all events, the move to China was cancelled, and Krayer was given tenure (as associate professor) and made head of the department. At this time, too, he married Erna Ruth Philipp and moved into the comfortable house in West Newton in which so many students and young colleagues and their families were to be entertained.

Another vignette, from the spring of 1939, epitomizes Krayer's readiness to do—instantly and without weighing consequences—whatever was needed when a worthy person or cause required help. The government of the Spanish Republic, led by the physiologist Juan Negrin, had been overthrown in a bloody civil war. Military support of the insurgents under Franco by Nazi Germany and Fascist Italy, and of the leftist government of the Republic by the Soviet Union, had made Spain a controversial political cause célèbre in the United States. The safe course, in university life as elsewhere, was to distance oneself from political controversy and to keep quiet.

Rafael Mendez (later a distinguished scientist at the National Institute of Cardiology in Mexico and recently appointed general coordinator of the National Institutes of Health there) arrived in the United States as a political refugee in April 1939. A young pharmacologist still early in his career, Mendez had been drawn into government service by Negrin, first as financial attaché in Paris and Washington responsible for procuring military hardware, later as undersecretary of the interior in charge of information and internal security, and finally as the Spanish consul at Perpignan in southern France with the sad task of directing the mass emigration of the defeated loyalists from Spain to France. Mendez had met Krayer only twice: once while a visitor in Trendelenburg's department in 1929 and once for a few hours in London in 1934.

Mendez tells how, after arriving in the United States, he wrote to several universities and pharmaceutical companies asking for a job, and received "many kind replies but no offerings." Then Walter B. Cannon (who was an ardent supporter of the Spanish Republic) learned that Mendez was in New York. "The next day," Mendez writes, "Krayer showed up at the modest hotel in which I was staying with my wife and four-month-old son, and two weeks later he received me hospitably in Boston appointing me Instructor and Research Associate. . . . Krayer took care of me as a loving father. . . ."

From December 7, 1941, Krayer found himself in the awkward position of "enemy alien." Among the inconveniences he had to endure was a restriction of his travel to a 25-mile radius of Boston, so he could not attend the annual meetings of pharmacologists and physiologists at the "Federation" in Atlantic City every spring. Nevertheless, the war years saw increasing productivity of his own research and the foundations laid for the very strong department that was ultimately to develop. Krayer's first Ph.D. student, Albert Wollenberger (now a professor at the Academy of Sciences of the

German Democratic Republic in Berlin), received his degree in 1946. Junior faculty in this early period (1941–1944) included George H. Acheson, Edwin B. Astwood, H. Stanley Bennett, Ralph W. Brauer, Sydney Ellis, Dale G. Friend, Bertrand E. Lowenstein, Harriet M. Maling, Rafael Mendez, Gordon K. Moe, Richard Tyslowitz, Willard P. Vander Laan, Jr., and Earl H. Wood. With the help of these colleagues—and later of Alfred E. Farah, Arthur J. Linenthal, Douglas S. Riggs, and the author—Krayer was able to implement a full-fledged laboratory course in pharmacology for all the medical students, on a larger scale than he had done in Beirut. With a class of 125 each year, this was a major logistic undertaking, carried out by the capable and loyal *Diener* Mr. George, with Mary Root as the first of a succession of graduate students assigned to this important task.

The day began with a pharmacology lecture to the whole class. And what Harvard graduate of those early years does not recall with nostalgic delight the quaint Germanisms like "Make dark, Mr. Chorge!" or "If you administer alcohol to a typewriter. . . ."? Following the lecture, one-quarter of the students, in rotation on successive days, trooped upstairs to the old barn-like student laboratory on the top floor of Building E. It may not be fully realized the extent to which the concepts and even the specific experiments carried out in this laboratory course at Harvard spread to other medical schools by word of mouth, by dissemination of the laboratory preparation manual, and by Krayer's people leaving to join (or establish) other departments. Thus by the middle 1960s the Krayer influence had made itself felt in pharmacology courses throughout the United States. Subsequently, to Krayer's dismay, laboratory teaching was abandoned in school after school, as faculty members succumbed to pressure from student activists, who saw this and the rest of basic science as largely "irrelevant."

The immediate postwar years saw Krayer in the role of

organizer—of relief efforts for the German university students and professors, and later as a member of the Unitarian Service Committee Medical Mission to Czechoslovakia (directed by Harvard cardiologist Paul Dudley White). In 1948 Krayer served as chairman of the medical mission to Germany under the same auspices. His precisely crafted, thoughtful, 21-page typewritten report makes interesting reading even today. The question was what should and could be done most effectively to help the reconstruction (intellectual, moral, and physical) of the German universities and of German biomedical science. Krayer's faith in young people was a constant theme of his life, and here it dominated his response to the catastrophe that had befallen his homeland. He wrote:

> Of the "lost" generation, grown up under Hitler and supposedly poisoned beyond hope by the Nazi teaching, not much if anything can be seen. This generation is not lost. On the contrary, many of these young people now in the first years of their university education became skeptical of the Nazi doctrine long before its fallacies and disastrous features began to dawn upon the older generations. If they find response and encouragement at home and abroad as well as appropriate and wise guidance, these young men and women will be the best guarantee for a "better" Germany.

The report made a series of concrete recommendations: study tours abroad for professors who had not been active Nazis, fellowships for younger scientists, reconstruction of libraries, provision of equipment and supplies to selected institutions, establishment of blood banks and plasma fractionation laboratories, and production facilities for antibiotics. But most important, in Krayer's view, was the maintenance and extension of the personal contacts that could help bring the German intellectuals back into the civilized world system.

> The greatest accomplishment of the Mission seems to me to be that for the first time since cultural and political ties between Germany and the

rest of the democratic western world were ruptured ten to fifteen years ago a large group of university members not connected with government and not having political motives have met with their counterparts in German universities on a basis of equality in the scientific field and with the aim and good will to establish friendly relations. . . . have shown the German colleagues that the possibility exists of ending their isolation from the rest of the world. . . .

An interesting side event of these years was the formation of the ill-fated Pharmacotherapy Committee at Harvard. President James B. Conant himself was a prime mover in this program for integrating research and teaching in pharmacology and therapy, with the hope of attracting major corporate and individual donors. Krayer saw in it an opportunity to develop an adequately large single department of pharmacology and pharmacotherapy. In this he anticipated later developments elsewhere, when clinical pharmacology programs with strong roots in basic science became popular. Krayer's memoranda concerning this committee reflect his long-standing interest in the clinical applications of pharmacology and his view that good therapists require a very solid training in basic pharmacology.

Internal disagreements frustrated the committee's work under the chairmanship of Professor of Medicine W. B. Castle. Krayer's failure to concur with plans that struck him as opportunistically donor oriented but scientifically unsound must have irked powerful committee members; his lack of suitability for the role of "team player" surely also made trouble. Abruptly, without consulting Krayer or the other members, Conant dissolved the committee. Not surprisingly, by 1947 we find Krayer again considering a move—this time to Basel—and with both Burwell and Conant actually urging him to leave. As matters developed, however, the Basel chair was given to an internal candidate, and Krayer remained.

The turn in his political fortunes at Harvard came dramatically with the retirement of Burwell, and a few years later, of Conant. George Packer Berry, who was to bring distinction to the Harvard Medical School in many ways, became dean in 1949. He immediately recognized what had been obvious to so many as a rank injustice unworthy of Harvard, and he moved to correct it. So in 1951, after fourteen years as associate professor, Krayer was finally promoted to full professorship. The years of the Berry deanship were flourishing ones for the Department of Pharmacology. Budgets at last grew, plans for reconstruction and expanded space took shape, and a swelling stream of students, trainees, junior faculty, and visiting scientists filled the department. Krayer's relationship with Berry became exceedingly close, and Krayer played an increasingly important part in the affairs of the school, to be recognized before long as one of the wise senior statesmen in the Longwood Avenue basic sciences "quadrangle." His public vindication (if it may be called that) came with his election to the National Academy of Sciences in 1964.

Krayer's style in discourse with his peers could be bluntly honest. An excerpt from his remarks at a meeting of the Preclinical Council sheds light on this tendency to speak the unvarnished truth:

> The task is to build a strong faculty around the HMS quadrangle. We are not, in my opinion, an exceptional group. There are probably half a dozen medical schools in the country who measure up to us or are stronger. . . . We cannot allow to let the reputation of HMS rest with past glory. . . . Let us not be concerned overly much with the problem of personality. . . . Certainly we are not assembled here to form a group of congenial people who have the foremost task of getting along superbly with each other.

Krayer's view of pharmacology was a broad one. Although his own research was wholly devoted to understanding drug action at the physiologic level—on the functions of organs

and organ systems—he nonetheless recognized and fully supported the most modern developments. He encouraged the new lines of experimentation by the young people in his department. I was one of the early beneficiaries of this enthusiasm for the newly developing fields of biochemical and molecular pharmacology. S. Ellis, F. L. Plachte, O. H. Straus, and I were able to apply enzymologic methods to studying the pharmacokinetics of cholinesterase inhibitors in dogs and in patients with myasthenia gravis (1943e; 1944a; 1949b), and in the course of those studies to discover some new principles about enzyme-substrate-inhibitor interactions. Krayer's interest was in learning how to quantitate the concept of "eserinization"—the blockade of the destruction of acetylcholine by inhibition of cholinesterases—in order to lay a basis for more rational treatment of myasthenic patients.

In like manner he foresaw the importance of behavioral pharmacology very early. He brought P. B. Dews into the department to establish a laboratory of behavioral pharmacology at a time when the pioneering techniques being developed across the river by B. F. Skinner had not yet been applied anywhere to studying the behavioral effects of drugs.

His plan and outlines for the ideal department he hoped to build reveal his belief that the strength of pharmacology lies in its cross-disciplinary breadth. To understand fully the action of a drug—usually through the joint efforts of several investigators—requires that the effects on whole organisms and their organ systems be related to the *relevant* biochemical and biophysical actions on cells and subcellular elements. He often ridiculed the reductionism that sometimes led to proposed mechanisms of drug action based on some test tube phenomenon at a concentration vastly higher than could ever be attained in vivo.

By 1960 the department had moved into new quarters, financed in part with funds provided by the National Insti-

tutes of Health in recognition of the national importance of this center for research and training in pharmacology. And in 1966, just before his retirement, Krayer's department was ranked first among all pharmacology departments in the nation by the American Council on Education.

Seeing the great future of neurobiology on the horizon, and recognizing quality wherever he saw it, Krayer had played the key role in bringing S. W. Kuffler and his colleagues from Johns Hopkins to Harvard. Putting the interests of the medical school ahead of the long-term needs of his own department, Krayer had set aside space for a laboratory of neurophysiology—"temporarily," as such arrangements are often planned to be at the outset. This statesmanlike action certainly brought glory to the Harvard Medical School (including, as it turned out, a Nobel prize), but there are those who argue (and Krayer discovered) that altruism can be a losing proposition amidst the intramural competitions of modern university life.

In the subsequent few years until his retirement, Krayer had to watch, painfully and helplessly, as the stage was set for the dismantling of the strong department he had built. The search for his successor was delayed repeatedly by fruitless philosophical debates about the role of pharmacology; meanwhile, other department heads made plans for possible uses to which one or another part of the pharmacology space could be put. Berry's retirement (in 1965) and Robert H. Ebert's accession to the deanship left pharmacology without an effective advocate. In January 1966, only seven months before his mandatory retirement, Krayer framed a letter of resignation, as a gesture of protest, and was only restrained from sending it by the insistence of his close colleagues that nothing could be accomplished that way. It is ironic, after his unquestioned research and teaching achievements and his

worldwide recognition for having built what was probably, on balance, the most important department of pharmacology in the world, that Krayer felt compelled to say to a group of his younger associates at this time: "Frankly, I am impressed more by what I missed or bungled than by what I recognized and resolved."

On August 31, 1966, having reached the mandatory age, Krayer retired to the red brick house in West Newton, and for the next five years he never once returned to Harvard Medical School. Here, under the great apple tree, and in the carefully tended garden with its medicinal plants (especially *Digitalis* and *Veratrum*), was where so many generations of medical students and young scientists had gathered for tea or to drink Rhine wine, and to experience Krayer's sincere interest in their welfare and their educational and scientific progress. Whenever small children were brought to these gatherings, Krayer's stern exterior dissolved. Toddlers would climb onto his lap, and older children took him by the hand. Ullrich Trendelenburg, the son of Krayer's chief at Freiburg and Berlin—a longtime Krayer associate and now professor of pharmacology at Würzburg—recalls this remarkable affinity for children, which he himself experienced as a small child. Trendelenburg writes:

> "Onkel Krayer" was very popular with us. He invariably wore a dark suit, and he was very quiet. Nothing of his considerable temper ever showed when he was with children. It was in 1948 when he visited. . . . he mentioned that lightning had struck his plane, my little nephew wanted to know why being struck by lightning was less dangerous for a plane than for a human being on the ground. Otto promptly turned his full attention to the child, and he gave a full (though slightly simplified) explanation; there was no attempt to "palm off" the inquisitive child. At that moment I realized that Otto had always been willing to give complete answers to our questions, quite in contrast to all those innumerable adults who were convinced that the child was unable to understand it in any case.

For the first six months after his retirement Krayer held the title of Special Consultant to the Dean, but Dean Ebert did not seek advice and by June the post was abruptly abolished. Continued proximity to events at Harvard depressed Krayer deeply. He and his wife began to travel, and in September 1971 they settled in Tucson. The Krayers found this part of the Southwest much to their liking—especially the mountains, where they enjoyed long walks and strenuous hikes. Krayer worked sporadically on a biographic and scientific history of the schools of Rudolf Buchheim (1820–1879) and Rudolf Boehm (1844–1926), pioneers of German pharmacology, but this work was never completed. Making the best of both climates, the Krayers spent winters in Tucson and summers in München. He held a visiting professorship at the University of Arizona School of Medicine and a similar appointment at the Technical University of München, where his former associate Melchior Reiter was professor of pharmacology.

Krayer's abiding devotion to young people (as though they were all surrogates for the children he himself never had) was expressed well in a letter written toward the end of his life. In it, Krayer thanks the faculty and staff at the Technical University of München for their good wishes on the occasion of his eightieth birthday:

> My dear young friends: Your good wishes, at the end of my 80th year, were a welcome present. You gave me the possibility—while I was living amongst you for some time—to get to know your academic work and, more than that, to share some part of your personal thoughts, joys, and sorrows. Contact and exchange of ideas with teachers, coworkers and students were especially close to my heart during the half century of my academic activity. Thanks to your confidence and your friendly inclinations towards me, I am allowed once more, so near to the end of my time, to experience some of the joy which is the source of a fruitful contact between the generations. I thank you for it.

In anticipation of Krayer's eightieth birthday, a celebration and two-day symposium were organized by Thomas F. Burks and his colleagues and held at Tucson in March 1978. There many of his younger associates gathered in a moving display of affection and admiration. The papers presented were later published in *Life Sciences* (22:1113–1372, 1978). At Harvard Medical School an Otto Krayer Lectureship had been established, and the Krayers journeyed to Boston to attend the first lecture, which was delivered on March 13, 1974, by the noted British physiologist Sir Bernard Katz. Subsequent Otto Krayer lecturers (through 1984) have been S. Ebashi, G. Burnstock, H. W. Kosterlitz, E. G. Krebs, J. R. Vane, H. Umezawa, J. W. Black, T. Lindahl, and Y. Nishizuka. In 1982 (posthumously), Harvard established the Otto Krayer Professorship of Pharmacology, the first incumbent of which was Krayer's successor as head of the department, Irving H. Goldberg.

No account of Krayer's life would be complete without noting his services to the American Society for Pharmacology and Experimental Therapeutics. His first major contribution, appropriately, was to serve for five years as associate editor of one of the Society's journals, *Pharmacological Reviews*. This was followed by another five years as editor-in-chief. The year 1957–1958 saw him in the role of president of the Society. He organized and conducted, with great dignity, the centennial celebration, at Johns Hopkins University, commemorating John Jacob Abel, the father of American pharmacology. Krayer worked tirelessly and successfully to acquire a physical home for the Society at Beaumont House in Bethesda, near the National Institutes of Health. He conceived and brought to fruition the Corporate Associates program, which brings financial support to pharmacology from the pharmaceutical and chemical industries. Posthumously,

in 1984, the Society that Krayer had served so well instituted the Otto Krayer Award in Pharmacology.

In 1980, after nine years of shuttling between Tucson and München, a macroglobulinemia of long standing progressed and became complicated by other conditions, so that the regimen of twice-yearly travel proved too taxing. Toward the end of 1981 Krayer's health deteriorated rapidly, a prostatic cancer being superimposed on the blood dyscrasia. Repeated hemodialyses and hospitalizations became necessary, he grew progressively weaker and more uncomfortable, and finally, at his own request, he was discharged from hospital to die at home in the care of his wife on March 18, 1982.

With Otto Krayer's passing the world lost one of the great pharmacologists of his time. But to those fortunate enough to have come under his influence he was much more than that. He will be remembered for the uncompromising standards he set—in research, in teaching, in ethical behavior. "Throughout the years," wrote U. Trendelenburg, "he has been the favourite of my younger coworkers. He set them something that is very rare nowadays—an example." Over the course of his thirty years at Harvard, Krayer trained, collaborated with, and set an example for an extraordinary number of scientists, a great many of whom became leaders in pharmacology throughout the world themselves. The names of these people are just as much Krayer's "bibliography" as the compendium of his own publications, and therefore it is appropriate that they be listed here. Represented are scientists from 26 foreign countries on 5 continents, as well as students, staff, and visiting scientists from the United States.

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|---|---|---|
| M. Abe | M. A. Aliapoulios | E. Amundsen |
| G. H. Acheson | A. A. Alousi | R. T. Anselmi |
| R. Aiman | M. H. Alper | L. Aronow |

R. B. Arora
E. B. Astwood
D. Atanackovic
V. Atanackovic
M. L. Bade
B. W. Baker
D. L. Bassett
T. Bayer
J. M. Benforado
H. S. Bennett
F. G. Bergmann
J. R. Blinks
J. L. Borowitz
R. W. Brauer
P. Braveny
F. N. Briggs
L. H. Briggs
W. S. Brimijoin
H. Büch
F. J. Bullock
W. R. Burack
E. A. Carr, Jr.
J. Chamberlain
A. Clark
J. S. Cohen
V. H. Cohn, Jr.
C. W. Cooper
G. L. Coppoc
P. J. Costa
J. R. Crout
H. Croxatto
P. C. Dandiya
G. S. Dawes
C. V. Deliwala
P. B. Dews
R. Di Nirjana
J. Dörner
B. Douglas
P. R. Draskoczy
A. J. Dunipace
S. Ellis
H. L. Ennis
V. Eybl
J. D. Falk
A. E. Farah
J. J. Fischer
W. E. Flacke
J. H. Fleisch
W. W. Fleming
J. M. Flynn
G. N. French
S. Friedman
D. G. Friend
M. E. Fuday
J. Fuentes
M.-P. I. Gabathuler
R. R. Garcia
J. M. Garfield
R. A. Gillis
A. Goldstein
B. Gomez (Alonso de la Sierra)
J. S. Gravenstein
P. K. Gujral
J. M. Hagen
P. B. Hagen
R. Hancock
L. S. Harris
K. Hashimoto
D. F. Hawkins
M. L. Heideman, Jr.
P. F. Hirsch
F. Hoffmann
B. Hofheinz
F. Honerjäger
F. A. Howard
A. M. Hughes
H. Ibayashi
A. Illanes
I. R. Innes
S. D. Iversen
O. Jardetzky
J. A. Jehl
B. R. Jewell
H. Jick
N. S. Johary
J. A. Johnson
G. R. Julian
R. Kadatz
A. J. Kaumann
R. T. Kelleher
A. D. Kenny
C. J. Kensler
D. Kessel
R. Kilpatrick
J. Koch-Weser
H. W. Kosterlitz
S. R. Kottegoda
K. Kramer
J. E. Krueger
S. M. Kupchan
S. Z. Langer
D. Lavie
F.-L. Lee
M. V. Leeding
T. H. Li
J. Liebman
A. J. Linenthal
W. K. Long
A. V. Lorenzo
B. E. Lowenstein
M. Lubin
U. C. Luft
G. K. MacLeod
W. A. Mahon
H. M. Maling
J. J. Mandoki

J. F. Marchand
G. Maresh
E. Marley
J. M. Marshall
M. L. Mashford
A. Matallana
H. M. Mazzone
R. J. McKay, Jr.
J. W. McKearney
D. E. McMillan
E. Meilman
C. Mendez
R. Mendez
M. D. Miller
B. A. Mitman
G. K. Moe
E. Moisset de Espanes
G. Montes
W. H. Morse
P. L. Munson
A. J. Muskus (Arevalo)
A. Nakamura
M. F. Narrod
P. Ofner
C. B. Olson
P. B. Ourisson
M. K. Paasonen
P. Pappas
A. F. Parlow
A. Pekkarinen
T.-C. Peng
S. A. Pereira
F. L. Plachte
R. Pluchino
S. B. Pluchino
L. T. Potter
M. Rabadija
S. Ramachandran
H. A. Ravin
H. W. Reas
M. Reiter
U. I. Richardson
D. S. Riggs
S. H. Robinson
B. H. Rogers
A. Roos
M. A. Root
C. O. Rutledge
H. J.-P. Ryser
J. K. Saelens
M. M. Saint-Paul
F. Sallmann
H. Schaer
I. Scheuling
J. Schmier
G. L. Schmir
H. R. Schröter
B. W. Searle
J. C. Seed
E. E. Seifen
G. W. G. Sharp
C. B. Smith
L. H. Smith
E. Sodi-Pallares
M. Speckert
J. B. Stanbury
J. D. Stoeckle
O. H. Straus
V. S. Subbu
C. R. Swaine
N. Taira
T. Tamai
K. Tanaka
A. H. Tashjian, Jr.
E. W. Thomas
P. J. Thomas
E. Thorogood
C. D. Thron
U. G. Trendelenburg
T.-H. Tsai
R. Tyslowitz
F. C. Uhle
W. Ulbricht
G. E. Vaillant
W. P. Vander Laan, Jr.
C. G. Van Dongen
M. van Leeuwen
E. F. Van Maanen
A. Vere
T. K. Wadhwani
M. B. Waller
A. B. Wasthed
J. M. Wattenberg (Sanpere)
D. R. Waud
N. Weiner
H. Wells
P. N. Witt
D. E. Wolfe
D. Wolff
A. Wollenberger
E. H. Wood
E. A. Wright
M. M. Wright
S. J. Yaffe
T. S. Yeoh
C. Yuan
B. Zimmermann

A few selected assessments by Krayer's trainees, coworkers, and academic colleagues may serve, collectively, as an appropriate epitaph with which to end this memoir.

**P. B. Dews:** "One of Krayer's great strengths was his absolute honesty and trustworthiness. When he advised a course of action, one could be quite sure that it represented his judgment of what was best for the individuals involved, untinged by what was best for Krayer. The complete loyalty to his colleagues and helpers engendered a reciprocal loyalty to himself. He was dedicated to the pursuit of excellence but did not believe this pursuit required a lack of consideration of others or ruthlessness. He confidently expected people to rise to excellence."

**P. R. Draskoczy:** "His integrity and high ethical standards combined with a special place in his heart for those who were suffering or deprived made him both strong and compassionate."

**D. S. Riggs:** ". . . a man of unflinching conscience and shining integrity, he set his associates—young and old—an example which none of us will ever forget."

**A. C. Barger:** "He was one of the few teachers in the medical school that I worshipped—for his superb pedagogic skills, his warm human qualities, and his willingness to fight for principles."

**B. D. Davis:** "Otto was for me the personification of academic integrity and dignity, and I often thought of his high standards of behavior as I watched the deterioration of standards that has been creeping into medical research in recent years."

**J. R. Blinks:** "He was, without doubt, the finest human being I have ever known."

I AM GRATEFUL to Mrs. Otto Krayer for making numerous source materials available to me and for helpful discussions about past events. Mr. Richard J. Wolfe, archivist at the Countway Library of Harvard Medical School, facilitated my access to Krayer's Harvard files. All original documents upon which this memoir was based can now be found at the Countway Library.

Ullrich Trendelenburg, Melchior Reiter, and Peter B. Dews furnished much useful information both in personal communications

and in their published obituary notices, which are listed at the end of these acknowledgments.

Many colleagues in the United States and abroad were helpful to me in large ways and small. Wilhelm Feldberg, G. Kuschinsky, and Marthe Vogt provided information and reminiscences about the Berlin years; and George Fawaz contributed material about the Lebanon period. For recollections of the early Harvard years, A. Baird Hastings and Eugene M. Landis graciously allowed me to impose on their time. My own memories were supplemented by those of Rafael Mendez and Douglas S. Riggs. Others who were helpful included George H. Acheson, John R. Blinks, Alfred E. Farah, Werner E. Flacke, William W. Fleming, Louis S. Harris, Werner F. Mosimann, Paul L. Munson, Matti K. Paasonen, Douglas R. Waud, and Norman Weiner. Some of those mentioned above commented on a draft of the manuscript and pointed out errors, but of course they have no responsibility for the final product. I am grateful to all my colleagues who helped so generously.

German texts of letters or articles have been translated freely here; the reader should consult the original documents for exact wordings. I had help with some of the translations, for which I thank Malcolm Brown, Louisa Laube, and Jean-Pierre von Wartburg.

Finally, for her invaluable and expert assistance at all stages of this project, I am indebted to my secretary, Sharon Fields.

## TESTIMONIAL AND OBITUARY ARTICLES

Otto Krayer zum 65. Geburtstag. 1965. Gewidmete Arbeiten erschienen, in *Naunyn-Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie,* Berlin, Heidelberg, and New York: Springer-Verlag. (Reprinted from 248:1–560; 249:1–528; 250:59–71.)

M. Reiter. 1964. "Otto Krayer zum 65. Geburtstag," *Die Medizinische Welt,* 48:2604–5.

U. Trendelenburg. 1964. "Zum 65. Geburtstag von Professor Dr. Dr.h.c. Otto Krayer," *Arzneimittelforschung,* 14:1171–72.

U. Trendelenburg. 1978. "Remembrances. Otto Krayer," *Life Sciences,* 22:1113–14.

M. Reiter and U. Trendelenburg. 1982. "In memoriam. Otto Krayer," *Naunyn-Schmiedebergs Archives of Pharmacology,* 320:1–2.

H. Raškova. 1982. "Otto Krayer 1899–1982," *Physiologia Bohemoslovaca,* 32:468–69.

P. B. Dews. 1983. "Otto Krayer: 1899–1982," *Trends in Pharmacological Sciences,* 4:143–46.

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P. B. Dews. 1983. "Otto Krayer 1899–1982," *Harvard Medical Alumni Bulletin,* 571:60–61.

## HONORS AND DISTINCTIONS

### DEGREES AND HONORARY DEGREES

1926 M.D., University of Freiburg
1942 M.A. (Honorary), Harvard University
1957 M.D. (Honorary), University of Freiburg
1962 M.D. (Honorary), University of Göttingen
1973 M.D. (Honorary), Technical University of München

### PROFESSIONAL APPOINTMENTS

1926 Assistant in Pharmacology, University of Freiburg (with P. Trendelenburg)
1928 Senior Assistant in Pharmacology, University of Berlin (with P. Trendelenburg)
1929 *Privatdozent* for Pharmacology and Toxicology, University of Berlin
1930 Acting Head, Department of Pharmacology and Toxicology, University of Berlin
1932 Professor Extraordinarius of Pharmacology and Toxicology (with W. Heubner), University of Berlin
1934 Rockefeller Fellow, University College, London (with E. B. Verney)
1934 Visiting Professor and Head, Department of Pharmacology, American University of Beirut
1936 Lecturer in Pharmacology, Harvard Medical School
1937 Associate Professor of Pharmacology, Harvard Medical School
1939 Associate Professor of Comparative Pharmacology and Head, Department of Pharmacology, Harvard Medical School
1951 Professor of Pharmacology, Harvard Medical School
1954 Charles Wilder Professor of Pharmacology, Harvard Medical School
1964 Gustavus Adolphus Pfeiffer Professor of Pharmacology, Harvard Medical School
1966 Gustavus Adolphus Pfeiffer Professor of Pharmacology, Emeritus, Harvard Medical School

MEMBERSHIPS

Deutsche Pharmakologische Gesellschaft (1927)
Deutsche Chemische Gesellschaft (1933, resigned 1937)
American Society for Pharmacology and Experimental Therapeutics (1938); President (1957–1958); Chairman, Board of Publications Trustees (1960–1962)
New York Academy of Sciences (1943); Fellow (1951); Life Member (1975)
American Association for the Advancement of Science (1944)
Society for Experimental Biology and Medicine (1944)
American Academy of Arts and Sciences (1949)
Pharmacological Society of Canada (1957)
National Academy of Sciences (1964)

HONORARY MEMBERSHIPS

Alpha Omega Alpha, Harvard Medical School (1943)
Society for Pharmacology and Therapeutics of the Argentinian Medical Association (1947)
Czechoslovakian Medical Society of J. E. Purkinje (1948)
Deutsche Pharmakologische Gesellschaft (1952)
British Pharmacological Society (1956)
Finnish Pharmacological Society (1961)
Deutsche Akademie der Naturforscher Leopoldina (1962)
Swiss Academy of Medical Sciences (1964)
Japanese Pharmacological Society (1972)

PROFESSIONAL AND PUBLIC SERVICE

Associate Editor, *Ergebnisse der Physiologie, biologischen Chemie und experimentellen Pharmakologie* (1933–1935, 1939–1976)
Treasurer, Boston Committee to Help German Scientists (1946–1948)
Member, Unitarian Medical Mission to Czechoslovakia (1946)
Chairman, Unitarian Medical Mission to Germany (1948)
Associate Editor, *Pharmacological Reviews* (1948–1953)
Member, Pharmacology Study Section, U.S. Public Health Service (1950–1954)
Consultant, Eli Lilly & Co. (1950–1956)
Editor-in-chief, *Pharmacological Reviews* (1953–1959)

Member, Scientific Advisory Committee, Massachusetts General Hospital (1959–1961)
Member, U.S. National Committee for the International Union of Physiological Sciences (1959–1965)
Special Consultant to the Dean, Harvard Medical School (1967)
Member, Editorial Board, *Annual Review of Pharmacology* (1967–1972)

## AWARDS AND HONORS

Order of the White Lion, Class IV, Republic of Czechoslovakia (1946)
Medal for Service to the University, Charles University, Prague (1946)
Commemorative Plaque, Czechoslovakian Medical Society (1946)
Honorary Citizen of Köndringen (1957)
Torald Sollmann Award of the American Society for Pharmacology and Experimental Therapeutics (1961)
Schmiedeberg Plakette of the German Pharmacological Society (1964)
Festschrift (65th Birthday), *Naunyn-Schmiedebergs Archiv für experimentelle Pathologie und Pharmakologie*, volumes 248–250 (1964)
Otto Krayer Lectureship at Harvard Medical School (established, 1966)
Research Achievement Award, American Heart Association (1969)
Otto Krayer Professorship of Pharmacology, Harvard Medical School (established posthumously, 1982)

## LECTURESHIPS

Mayo Foundation Lecturer, Rochester, Minnesota (1947, 1952)
University Lecturer, Aberdeen, Scotland (1955)
Litchfield Lecturer, University of Oxford, England (1955)
Special Lecturer, University College, London, England (1955)
Fahr Lecturer, University of Minnesota (1956)
University Lecturer, Helsinki, Finland (1961)
A. N. Richards Lecturer, Physiological Society of Philadelphia (1962)
Visiting Lecturer, Tohoku Medical Society, Sendai, Japan (1965)

Visiting Centennial Professor of Pharmacology, Howard University Medical School (1966)
Visiting Professor of Pharmacology, Stanford University (1968)
Visiting Professor, Department of Pharmacology, Technical University of München (1972–1980)
Visiting Professor, Department of Pharmacology, College of Medicine, University of Arizona (1972–1980)

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1926

O. Krayer. Die pharmakologischen Eigerschaften des reinen Apokodeins. Arch. Exp. Pathol. Pharmakol., 111:60–67.

1928

a. O. Krayer and G. Sato. Schilddrüsenwirkung und autonomes Nervensystem. Arch. Exp. Pathol. Pharmakol., 128:67–81.
b. O. Krayer. Über Verteilung und Ausscheidung des Jodes nach Zufuhr von Schilddrüsenstoffen. Arch. Exp. Pathol. Pharmakol., 128:116–25.

1929

O. Krayer. Die akute Kreislaufwirkung des Neosalvarsans. I. Mitteilung: Die Analyse der Kreislaufwirkung. Arch. Exp. Pathol. Pharmakol., 146:20–43.

1930

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b. O. Krayer. Über die Beziehung zwischen Pulsfrequenz, Minutenvolumen und Venendruck am isolierten Saügetierherzen. Verh. Dtsch. Pharmakol. Ges., 157:90–91.

1931

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b. O. Krayer. Die Physiologie der Coronardurchblutung. Verh. Dtsch. Ges. Inn. Med., XLIII. Kongress Wiesbaden, 237–47.
c. O. Krayer. Paul Trendelenburg. Arch. Exp. Pathol. Pharmakol., 162:III–IX. (Obituary.)
d. O. Krayer. Versuche am insuffizienten Herzen. Arch. Exp. Pathol. Pharmakol., 162:1–28.
e. O. Krayer and A. Rühl. Über die Wirkung einer reinen Gefässerweiterung auf den Gesamtkreislauf. Arch. Exp. Pathol. Pharmakol., 162:70–85.

f. O. Krayer. Der toxikologische Nachweis des Coniins. Arch. Exp. Pathol. Pharmakol., 162:342–72.
g. O. Krayer and W. Koll. Coniinähnliche Eigenschaften einiger Aminbasen. Arch. Exp. Pathol. Pharmakol., 162:373–84.
h. *P. Trendelenburg's Grundlagen der allgemeinen und speziellen Arzneiverordnung,* 3d ed. rev. O. Krayer. Berlin: Springer.

1932

a. O. Krayer. Über die Behandlung von Kreislaufstörungen mit Organ- und Muskelextrakten. Bemerkungen zur Pharmakologie. Dtsch. Med. Wochenschr., 58:123–24.
b. O. Krayer and E. Schütz. Mechanische Leistung und Aktionsstrom des Warmblüterherzens. Verh. Dtsch. Pharmakol. Ges., XI. Tagung, 99–100.
c. O. Krayer and E. Schütz. Mechanische Leistung und einphasisches Elektrogramm am Herz-Lungen-Präparat des Hundes. Z. Biol., 92:453–61.

1933

a. O. Krayer. Ist die Integrität der sympathischen Schilddrüseninnervation notwendig für die thyreotrope Wirkung des Hypophysenvorderlappens? Arch. Exp. Pathol. Pharmakol., 171:473–79.
b. W. Feldberg and O. Krayer. Nachweis einer bei Vagusreiz freiwerdenden azetylcholinähnlichen Substanz am Warmblüterherzen. Verh. Dtsch. Ges. Kreislaufforsch, VI. Tagung, 81–83.
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1934

a. F. Grabe, O. Krayer, and K. Seelkopf. Beitrag zur Aufklärung der kreislaufwirksamen (adrenalinähnlichen) Stoffe in Leberextrakten. Klin. Wochenschr., 13:1381–83.

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1935

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b. O. Krayer and E. B. Verney. Reflektorische Beeinflussung des Gehaltes an Acetylcholin im Blute der Coronarvenen. Arch. Exp. Pathol. Pharmakol., 180:75–92.

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1938

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c. O. Krayer. Action of *l*-ascorbic acid upon the isolated frog heart. Proc. Soc. Exp. Biol. N.Y., 53:51–52.
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c. A. Farah and O. Krayer. The action of dimethylaminoethanol upon the heart-lung preparation of the dog. Fed. Proc. Fed. Am. Soc. Exp. Biol., 5:177–78.

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1949

a. O. Krayer, S. B. Wolbach, J. H. Mueller, and G. B. Wislocki. Reid Hunt. Harv. Med. Alumni Bull., 23:39–42. (Obituary.)
b. A. Goldstein, O. Krayer, M. A. Root, G. H. Acheson, and M. E. Doherty. Plasma neostigmine levels and cholinesterase inhibition in dogs and myasthenic patients. J. Pharmacol. Exp. Ther., 96:56–85.
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f. O. Krayer. Studies on veratrum alkaloids. IX. The inhibition by veratrosine of the cardioaccelerator action of epinephrine and of norepinephrine. J. Pharmacol. Exp. Ther., 97:256–65.
g. O. Krayer and E. F. Van Maanen. Studies on veratrum alkaloids. X. The inhibition by veratramine of the positive chronotropic effect of accelerans stimulation and of norepinephrine. J. Pharmacol. Exp. Ther., 97:301–7.
h. O. Krayer. The pharmacological basis for the use of veratrum alkaloids in the treatment of hypertension. Proc. Rudolf Virchow Med. Soc. City N.Y., 8:126–27.

1950

a. *Lectures—Unitarian Service Committee Medical Mission to Germany, July 2–September 3, 1948*, ed. O. Krayer. Berlin: Springer.
b. E. Meilman and O. Krayer. Clinical studies on veratrum alkaloids. I. The action of protoveratrine and veratridine in hypertension. Circulation, 1:204–13.
c. O. Krayer. A quantitative comparison of the antiaccelerator action of veratramine and jervine. J. Pharmacol. Exp. Ther., 98:19.
d. K. Kramer, U. Luft, and O. Krayer. Action of epinephrine and veratramine upon heart rate and oxygen consumption in the

heart-lung preparation of the dog. Fed. Proc. Fed. Am. Soc. Exp. Biol., 9:292.

e. M. Reiter and O. Krayer. Jervine and pseudojervine, antagonists to the cardioaccelerator action of epinephrine and of accelerans stimulation. J. Pharmacol. Exp. Ther., 98:27.

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g. O. Krayer. Studies on veratrum alkaloids. XII. A quantitative comparison of the antiaccelerator cardiac action of veratramine, veratrosine, jervine and pseudojervine. J. Pharmacol. Exp. Ther., 98:427–36.

h. O. Krayer. Solanum alkaloids with antiaccelerator cardiac activity. Fed. Proc. Fed. Am. Soc. Exp. Biol., 9:292.

i. O. Krayer and L. H. Briggs. Studies on solanum alkaloids. I. The antiaccelerator cardiac action of β-dihydrosolasodine and tetrahydrosolasodine. Br. J. Pharmacol., 5:118–24.

j. O. Krayer and L. H. Briggs. Studies on solanum alkaloids. II. The antiaccelerator cardiac action of solasodine and some of its derivatives. Br. J. Pharmacol., 5:517–25.

k. O. Krayer. The antiaccelerator cardiac action of quinine and quinidine. J. Pharmacol. Exp. Ther., 100:146–50.

l. O. Krayer. Untersuchungen über die Kreislaufwirkung der Veratrumalkaloide. Arch. Exp. Pathol. Pharmakol., 209:405–20.

1951

a. J. J. Mandoki, C. Mendez, R. R. Garcia, and O. Krayer. The action of veratramine and epinephrine on the functional refractory period of A-V conduction. J. Pharmacol. Exp. Ther., 101:25.

b. O. Krayer. Quinine-like action of veratramine upon the single twitch and upon the "veratrine response" of the sartorius muscle of the frog. Fed. Proc. Fed. Am. Soc. Exp. Biol., 10:316.

c. O. Krayer, F. C. Uhle, and P. Ourisson. Studies on veratrum alkaloids. XIV. The antiaccelerator cardiac action of derivatives of veratramine and jervine and of synthetic steroid secondary

alkamines obtained from pregnenolone and from sapogenins. J. Pharmacol. Exp. Ther., 102:261–68.

d. O. Krayer and H. W. George. Studies on veratrum alkaloids. XV. The quinine-like effect of veratramine upon the single twitch and upon the "veratrine response" of the sartorius muscle of the frog. J. Pharmacol. Exp. Ther., 103:249–58.

e. O. Krayer, J. J. Mandoki, and C. Mendez. Studies on veratrum alkaloids. XVI. The action of epinephrine and of veratramine on the functional refractory period of the auriculo-ventricular transmission in the heart-lung preparation of the dog. J. Pharmacol. Exp. Ther., 103:412–19.

1952

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b. R. B. Arora, E. Meilman, and O. Krayer. Action of veratramine and of sympathomimetic amines upon the automaticity of the atrio-ventricular node. Fed. Proc. Fed. Am. Soc. Exp. Biol., 11:318.

c. P. Ourisson and O. Krayer. Antagonistic action to the cardio-accelerator effect of ephedrine, synephrine, isuprel, tuamine and oenethyl. Fed. Proc. Fed. Am. Soc. Exp. Biol., 11:381.

d. O. Krayer. Antiaccelerator cardiac agents. J. M. Sinai Hosp. N.Y., 19:53–69.

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