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REVIEW OF REVUES

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As one accumulates years, deservedly or not, honor becomes one of the fruits of maturity. To write the prefatory instead of the final chapter of this volume tells me that some people with a strong bias (former students and close associates) believe I have some things worth relating, but this account is hardly an autobiography.

If I have received some credit as a mover perhaps my environment helped because I spent most of my life bordering earthquake faults. I was born in 1916 and attended elementary school in Watsonville, California, before moving in 1927 to San Francisco, where I received junior and senior high-schooling. My undergraduate and graduate degrees were awarded from the University of California at Berkeley, but in actuality I spent more than one half the time on the San Francisco campus, which was then administratively under President Robert Gordon Sproul. Except for six months in industry and one year in government, my career has been associated with academia. This includes more than four decades at UCSF, five years at George Washington University, and one year stints abroad in Switzerland, Hong Kong, and Japan, at universities with respective names Berne, Hong Kong, and Gunma. Anecdotes and experiences over this span have been chronicled to express my feelings and views for what they are worth.

TEACHERS

To learn has always been fun but I had many teachers to stimulate and nourish my interests. Some teachers are able to impart a bit extra that helps pupils learn. One teacher's admonition has stuck in my mind, "Always remember

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that in May 1927, when you were in Miss Dempsey's fifth grade class, Charles Lindberg flew across the Atlantic." However, even before attending school, my parents tried to instill in their eight children the need for a good education. Like most immigrants with little formal learning, their future was in the success of their offspring and they labored long and hard to achieve this end. All of us went to college and three received advanced degrees. Once we started school our parents ceased displaying affection. They took it for granted that we would do well and seldom lavished praise. If we were punished, most of the time there was a basis, but even when not we did not question their right to do so; nor did we doubt their underlying love.

Even though learning was exciting and enjoyable, I have had a succession of teachers who modified the experiences by providing different types of stimulus. I was bamboo-switched in the first grade, belt-strapped in the second, and ruler-spanked in the fifth. Although I concede that I learned in these classes, I firmly believe that I did better in the third and fourth grades without the benefits of corporal punishment. Two very special pedagogues had a major impact on my life, my seventh grade teacher, Adeline Scandrett, and my university professor, Chauncey Leake. Adeline provided the nourishment and Chauncey the inspiration.

Adeline was a beautiful blue-eyed blond in her mid-twenties when luck placed me in her junior high school class. She was both my mathematics and registry teacher. The latter assignment made her the recipient of complaints from other teachers bedeviled by my pranks. Adeline was my staunch defender when twice I was scheduled for disciplinary action for fighting in the classroom. Once, she prevented me from being dropped from the honor roll by my vocation teacher and on another occasion from being kicked out of school by my music teacher. Although I was also a smart aleck in Miss Scandrett's class, she tolerated me—I guess because I performed well in math. Whenever I became overly exuberant she "punished" me by making me sit at her feet while she conducted class. I grew up in a tough neighborhood and might easily have taken the wrong path, but she channeled my sometime misguided energies into becoming a cheer leader. Her ability to control a raucous bunch of budding teen-agers with even-tempered rebuffs was extraordinary. Pupils just did not wish to be criticized by a respected, well-liked teacher and many remained in touch with her long after graduating. I still make it a point to visit her and finally, after sixty years, got a chance to kiss my teacher. I'll tell you more about her later.

Chauncey made me a pharmacologist even though he once bawled me out for sleeping in class. At the time, he was only forty but he seemed much older and formidable because of his silver hair, booming voice, and erudition. I was terrified and ducked hurriedly out of the classroom when the hour ended. Chauncey never forgave me because he forgot all about the incident. Later, as

a graduate student, I would on occasion attend pharmacology seminars where Chauncey led but never dominated the discussions. He constantly encouraged interaction among the attendees. His enthusiasm for novel ideas and his capacity for amazement at new discoveries were highly contagious. Graduate students were given free rein to attack their research problems. Although Chauncey's forte was not in the experimental approach and design, his insight, knowledge of the literature, and support were ever helpful and a source of inspiration. His tolerance of and loyalty to his disciples were almost to a fault but he was rewarded by intense reciprocation and deep affection. One of my most satisfying experiences as a departmental chairman was to establish the Chauncey Leake lectureship on his eightieth birthday; he continued to attend this function until he died in 1978.

My account of my two favorite teachers is not quite finished. I never thought their paths would cross, especially since Chauncey left San Francisco in 1942. He had accepted the Vice Presidency at the University of Texas to head the Medical Branch at Galveston. Then, after another stint and retirement at Ohio State University, he returned to UCSF in 1964 to accept the invitation of the Chairman of Pharmacology, Bob Featherstone, to coordinate graduate affairs. Chauncey and his wife Elizabeth were patrons of the arts and season-ticket holders for the symphony and opera series. A lovely pert lady had an adjacent seat and it is only natural that these repeated encounters led to casual social amenities. When Scandrett asked the silver-haired gentleman what he did for a living his reply prompted her to ask him if he knew Eddie Way. As a result, she invited me, Madeline, Chauncey, and Elizabeth for dinner where everybody except me addressed her as Adeline. Since I knew her the longest, I requested permission to address her likewise and even got a kiss on departing. Now, I ask, how many of you get to kiss your seventh grade teacher?

There is a saying that it is a poor student who does not excel his teacher but I would add that it is a poor teacher who does not learn from his pupils. I rather enjoy basking in reflected glory and derive pride and satisfaction in the success of former students, postdoctoral fellows, and scholars who became associated with my laboratory. Those who carved careers in academic pharmacology include Chen-yu Sung, Terry Adler, Jim Fujimoto, Aki Takemori, Bob George, Vee Sutherland, Nick Plotnikoff, John Kemp, Pushkar Kaul, Norio Kokka, Shi-chia Lin, Gladys Friedler, Horace Loh, Barry Berkowitz, Grant Wilkinsen, Adron Harris, Ing Kang Ho, Hemendra Bhargava, Edgar Iwamoto, Ray Quock, Dave Brase, Eddie Wei, and Larry Masten. Others like Barry Berkowitz, Bill Schmidt, and Stella Chao are doing well in industry, while Harvey Kupferberg, Khursheed Asghar, and Carol Glasgow have active important roles in government. Foreign scholars include Jens Schou, Abdel Afifi, Juan Pablo Huidobro-Toro, Kaito Tsurumi, Kohji Yoshi-

mura, Hiroaki Yamamoto, and Yoshio Yamasaki, Ikuo Yamamoto, David Chapman, Kang Tsou, Jean Hu, and Ahmad Rezvani. Nancy Lee, John Holaday, Bob Hitzeman, Tae Mook Cho, and Ping Yee Law more or less adopted me as godfather in the seventies when they became dependent on opiate research. Some medical students like Lloyd Old, Ken Melmon, Ron Okun, Walter Way (blond bald-headed son—no genetic relationship), Collin Quock, Fu-Shiung Shen, Ben P. N. Mo, Joe Asling, Joe Young, and Dirk van Peenen became successful in clinical fields.

RESEARCH

Most of my investigative work has been in the areas of drug metabolism and mechanisms in opiate tolerance and dependence development. However, I played the field before settling down. My earliest publications were concerned with the synthesis of organic arsenicals for antiprotozoan activity. I was the first student to enroll for graduate study in pharmaceutical chemistry at UCSF, receiving the MS in 1940 and the Ph.D. in 1942. Under my preceptor, John Oneto, who instilled in me the importance of careful methodology and keeping accurate notes, I synthesized some seventy-five new compounds. At the time penicillin was unknown, arsphenamine (compound 606) was the treatment of choice for syphilis, and there was much excitement about a new antibacterial, sulfanilamide. As a consequence, I prepared arsenic derivatives that incorporated the sulfonamide moiety in the hope of developing agents with trypanocidal and spirochetal activity.

To test the compounds, I consulted Chauncey Leake, together with a fellow graduate student, Leonard Chan, but we did not finish the project because our studies terminated and we left the UCSF campus in 1942. I did not complete the study until 1947 when I was at the George Washington University.

In between these two periods, I had accepted a position at Merck Company in Rahway, New Jersey, where I was assigned to enhance the stability of vitamins B_1, C, and niacinamide in sugar. This type of work did not seem too essential for the war effort so after a few months I was glad to leave and accept an instructorship in pharmacology.

In truth, I did not consider myself to be a pharmacologist and was most surprised to hear from George Roth who chaired the Department of Pharmacology at the George Washington University. Lucky for me, in those times the buddy system prevailed and there were no search committees. Chauncey, of course, had recommended me for the job. Even though I knew little pharmacology and the pay was considerably less than at Merck, I accepted Dr. Roth's offer immediately. It would be much more satisfying to help develop soldiers and sailors for future military service as physicians. The first year was most difficult since I had to help supervise the laboratory classes

and set up the demonstrations. I had very little experience in handling animals and had to learn pharmacology in the evenings before the next class.

Pharmacology was taught for only one semester so the rest of the year was free for pursuing research. I completed my study assessing the sulfo-arsenicals that I had prepared for trypanocidal activity. On finding the results disappointing, I floundered on what to do next.

One day I innocently asked Dr. Roth about the atropine-like properties of isonipecaine, which is known today as meperidine or pethidine, whether it might block vagal action. He replied, "Why don't you study it, doctor?" I demurred and thought I had put him off, but a few days later Dr. Roth informed me that the turtles and frogs for my research project had arrived. I got the message.

I found that meperidine not only inhibited the vagus but also had local anesthetic properties. This led me to believe it was a great discovery and I submitted a paper to *Science* that, surprisingly, was accepted for publication in 1945. The local anesthetic properties of isonipecaine prompted me to study its cardiac effects. Together with Bill Ligon, we reported in 1945 that it elevated the threshold for eliciting premature systoles and stopped experimental auricular fibrillation. I persuaded an internist to study the effects of meperidine on ventricular tachycardia. It worked well on the first two patients but not on subsequent ones and my career as a cardiovascular pharmacologist was more or less terminated.

Roth retired in 1945 and was succeeded in 1946 by Paul K. Smith. P.K. was a product of Yale and a contemporary of Louis Goodman and Alfred Gilman. As a colonel in the army P. K. was greatly influenced by Jim Shannon and B. B. Brodie and their studies on the biodisposition of antimalarials. Because of my background and training, it was no problem for me to get interested in drug metabolism. In those days, there were no GC mass chromatographs to get the job done. After purifying the parent compound in tissue fluids, colormetric methods had to be developed for its estimation.

Dr. Smith provided me with a suitable project and the funds to carry it out. P-amino-salicylic acid (PAS) had just been introduced for the treatment of tuberculosis. P.K.'s main interest was in the biodisposition of salicylates so he told me to study the fate of PAS. I developed a procedure for PAS by modifying the Bratton-Marshall method for aromatic amines and reported on its absorption, distribution, and excretion in humans. The paper gave me considerable satisfaction not only because it was my first publication in drug metabolism, but also because it appeared just before Marshall reported on a method for detecting PAS in biologic fluids.

At George Washington University, together with my first graduate student C. Y. Sung, we found that meperidine was metabolized by the liver to an unknown basic metabolite. Based on these preliminary data, I applied for and

was awarded a research grant in 1948 from NIH to study the biologic disposition of morphine and its surrogates. I transferred the grant when I moved to the University of California at San Francisco in 1949. With competing renewals, I held the grant for more than 20 years until I shifted to studying opiate tolerance and dependence mechanisms.

The proximity of UCSF to the Berkeley campus facilitated the acquisition of N-$^{14}CH_3$ labeled isotopes of meperidine, morphine, and codeine and this gave us a running head start over other investigators in this area. N-demethylation was found to be a common metabolic pathway for the surrogates of morphine. In actuality, this turned out to be a relatively minor pathway for opiates but it provided a major stimulus for studies on microsomal metabolism. N-demethylation also paved the way for two imaginative hypotheses: Beckett developed a theory of analgesia based on N-demethylation and Axelrod and Cochin postulated N-dealkylation as a mechanism for tolerance. Adler and I pointed out the defects of both hypotheses, but Axelrod's later works merited Nobel acclaim.

Nick Plotnikoff outlined several metabolic pathways of meperidine without actual isolation of any of the metabolites by using a nonspecific dye technique for his estimations. By combining the Brodie methyl orange procedure for organic bases with countercurrent distribution, Plotnikoff identified meperidine and normeperidine in the urine by their partition behavior. He then showed by application of esterification and hydrolysis procedures that meperidinic acid, normeperidinic acid, and their conjugated products were also present in the urine as biotransformation products. Burns, Brodie et al confirmed these studies and their paper was cited much more often than ours.

Another pathway established for some opiates was O-dealkylation. Terry Adler was the first to demonstrate in 1951 that codeine could be O-demethylated to morphine. To establish this point, O$^{14}CH_3$ labeled morphine was shown to yield $^{14}CO_2$ after parenteral administration of codeine and morphine was unequivocally identified by X-ray diffraction studies as a urinary metabolite of codeine. Together with Jim Fujimoto, we also found that codeine and morphine were N-demethylated to their respective nor derivatives, and norcodeine and normorphine would then be excreted in the urine as conjugates of glucuronic acid. In those days, it was not so simple to demonstrate glucuronide products of opiates because their high water solubility made their purification and isolation from urine by solvent extraction difficult. Oberst first demonstrated that the yield of morphine in the urine of morphine addicts could be increased substantially by acid hydrolysis, but not until almost 20 years later did Fujimoto show that the "bound" morphine in human urine was a glucuronide.

With Sung and Peng we found that methadone is N-demethylated but we had difficulty isolating and identifying the des-methyl metabolites, and it

remained for Pohland and associates to demonstrate that following mono- and didemethylation, the products undergo rearrangement to form cyclic metabolites. In studies on l-acetyl-methadol, Sung and I reported in 1954 that l-acetylmethadol undergoes extensive biotransformation and that much of its activity results from the formation of an active metabolite. The compound has the acronym LAAM and has been under investigation for maintenance of heroin addicts for what seems an eternity. Perhaps the FDA will finally give its approval.

In 1955, taking a sabbatical leave at Berne with Walter Wilbrandt to study the disposition of heroin, I was able to confirm that heroin is rapidly hydrolyzed to morphine. Later, with John Kemp and others, we found that the biologic half-life of heroin was less that 3 minutes and that the sequence of hydrolysis involved deacetylation first to 6-monoacetylmorphine and morphine. After subcutaneous, intravenous, and intracercbral injection, we found that morphine was least potent by the subcutaneous route but most potent after intracerebral injection. We concluded from these findings that the primary effects of heroin are due to the formation of morphine. The greater potency of heroin over morphine by the parenteral routes could be explained by the lipid solubility conveyed by the acetyl groups, which are then rapidly removed by esterases in the brain. Thus hydrolysis of heroin to morphine in the central nervous system represents an activation process, but when it occurs outside the brain in other organs or tissues, hydrolysis reflects a detoxification process.

The results of these studies let us to consider that the enhanced sensitivity of the newborn to morphine might be attributable to disposition factors. The toxicity of morphine in the rat was studied from birth to one month of age with Kupferberg. The LD50 remained relatively constant for 16 days but between days 16 and 32 it increased abruptly by fourfold. After developing a sensitive spectrophotofluormetric technique for measurements of brain morphine levels in the newborn with Al Burkhalter, we found that with equal doses of morphine the brain levels in the 16-day-old rat were usually more than twice those in the 32-day-old rat; to attain comparable brain levels with the two age groups it was necessary to administer a dose three times as high in the 32-day-old mice. Thus, the results provided an explanation for the difference in toxicity of the two age groups and indicated that the decreased sensitivity to morphine in the maturing animal is due in large part to the development of a blood-brain barrier to morphine. Subsequent studies with heroin and meperidine further revealed that this process was peculiar to morphine. Virtually no barrier development to heroin or meperidine could be demonstrated with increasing age and this was reflected by only small variations in toxicity between different age groups. My academic son, Skip Way, and Costley were able to confirm the findings in newborn infants. Permission

to carry out the study was granted only after a dispute between obstetricians and pediatricians on whether babies experienced pain while being circumcised was settled in our favor.

With Kaul, Lin, El Mazati, Afifi, Nayak, Berkowitz, and others we also studied the disposition of apomorphine, anileridine, noscapine, methotrimeprazine, and pentazocine and made generalizations concerning the disposition characteristics of basic compounds. Basic drugs are in general more potent than acidic ones because at body pH, proportionately more of the base exists in the unionized form. This property favors their gaining access to target sites for eliciting pharmacologic effects promptly and for sequestering in indifferent organs for later release to prolong drug action. By and large, organic bases, including the opiates, have a high apparent volume of distribution because they rapidly leave the blood and concentrate in parenchymatous tissues. Tissue levels can be decreased and excretion facilitated by lowering body pH. These conclusions were summarized and published in a 1962 monograph, *Biologic Disposition of Morphine and Its Surrogates,* with Terry Adler as coauthor.

In 1962 I took a second sabbatical leave and went to Hong Kong to assess the unique modes of inhaling heroin. Addicts there use two techniques: one is by smoking heroin inserted into a cigarette ("ack ack") and the other procedure is by inhaling the fumes resulting from heating a mixture of heroin and barbital ("dragon chasing"). I was informed that dragon chasing was a more effective way of inhaling heroin than ack ack. To find an explanation for this difference, Ben Mo and I decided to compare the urinary excretion of morphine by the two inhalation techniques with that after intravenous administration. Based on the percent of the dose that could be accounted for in urine, the efficiency of dragon chasing was found to be two-fifths that of intravenous injection and twice that of ack ack. At a high temperature such as that of a burning cigarette (746°C), availability of heroin is poor because of extensive decomposition. Barbital minimizes the loss of heroin by facilitating its volatilization at a lower temperature (644°C). It would appear that the Hong Kong junkies had as "connection" a pharmacist with a sophisticated knowledge of delivery systems. This technique was a prelude to the preparation of crack cocaine for inhalation.

Although most of our initial work centered on drug disposition studies some of my associates involved me in characterizing sites of opiate action. There is much current interest in the hypothalmic effects of β-endorphin and these studies relate back to some early work on morphine and hypothalamo-pituitary-adrenal function. In the 1950s, Bob George and I reported that the hypothalamus is an important intermediary for pituitary-adrenal activation by analgetic agents and that their effects could be blocked by a lesion in the median eminence. Subsequently, Bob George and Norio Kokka further noted

that growth hormone and gonadotrophin release are also altered by morphine. More recently, Eddie Wei (my "friends" identify him as the young, good-looking one) found that several mesodiencephalic areas of the brain, and the medial thalamic region in particular, are important for mediating opiate antinociception and certain withdrawal signs. Also, Edgar Iwamoto has demonstrated that nigrostriatal pathways are much involved in the expression of abstinence.

In 1966, I was invited to attend an International Symposium on analgetics in Santiago, Chile. There I met Professor F. Huidobro and observed his morphine pellet implantation technique for producing morphine tolerance and physical dependence in mice. In his earlier writings, Nathan Eddy had mentioned that tolerance and physical dependence did not develop in rodents, but, as it turned out, the earlier workers simply did not administer morphine frequently enough. I was fascinated by the simplicity of the pellet procedure and reflected that I could now study tolerance and physical dependence mechanisms without foregoing my week-end golfing activities. The pellet made by Professor Huidobro did not suit our needs because too limited quantities could be provided by a hand press. I consulted Bob Gibson in the School of Pharmacy. He and Tingstad formulated a tablet that could be mass produced and this pellet is now in wide use.

The implantation of a morphine base pellet subcutaneously in a mouse produces a high degree of tolerance and physical dependence in three days. A quantitative measure of the degree of tolerance development is given by an increase in the dose of morphine required to produce analgesia and this is generally between 7- and 20-fold. The degree of physical dependence can be quantified by determining the naloxone ED50 to precipitate withdrawal jumping, the greater the dependence the lower the naloxone ED50. I consider this 1969 study with Loh and Shen one of the more important contributions from my laboratory because it provided a quantitative approach for assessing opiate tolerance and physical dependence, as well as evidence suggesting a close relationship between the two phenomena.

Applying these procedures together with some pharmacologic probes, we initiated studies on the mechanisms involved in tolerance and physical dependence development. We obtained considerable evidence supporting the biochemical nature of these processes. Loh, Shen, and I were able to demonstrate blockade of tolerance development with inhibitors of protein synthesis and the development of physical dependence as well. It was also possible to achieve this effect without altering the acute actions of morphine. We postulated, therefore, that the macromolecule involved in tolerance and dependence development may differ from the receptor concerned with acute effects and was probably turning over at a more rapid rate. More recent findings in many laboratories indicate that the action of opiates involves different

recognition sites, second messenger systems and effectors, and tolerance development involves sequential stages that include desensitization, down regulation and nuclear protein synthesis.

Virtually every known putative neurotransmitter has been assessed with respect to its effect on the acute and chronic action of morphine. We (including Shen, Loh, Ho, Bhargava, Friedler, Iwamoto) and others have used various pharmacologic tools to affect as selectively as possible the synthesis storage, release, or degradation of acetylcholine, dopamine, norepinephrine, and serotonin, and the consequences of such maneuvers on the tolerant-dependent state and on the development of tolerance to and dependence on morphine were evaluated. We concluded that such substances may participate in the expression of acute pharmacologic responses to morphine as well as certain withdrawal signs in dependent animals but seem not to be primarily involved in triggering the development of tolerance to and physical dependence on morphine. We conjectured that a common mechanism that might alter ion flux would well be involved.

Extensive studies were then carried out on Ca^{++}-opiate interactions in the acute and chronic states and we offered a postulate to explain opioid action. A lowering of the Ca^{++} results in acute effects such as analgesia, whereas elevating Ca^{++} opposes acute effects to produce tolerance. For example, morphine and other opiates have been well established to lower neuronal Ca^{++}; other agents such as lanthanum, which reduces Ca^{++} uptake, and EGTA, which chelates Ca^{++}, also exhibit antinociceptive activity. On the other hand, the intraventricular injection of Ca^{++} produced hyperalgesia and antagonized morphine analgesia. Ca^{++} also greatly reduced the agonist effects of normorphine and β-endorphin on the guinea pig ileum. Moreover, the ionophore X537A, which facilitates Ca^{++} entry, augments Ca^{++} antagonism of morphine analgesia, whereas La^{+++} reverses the antimorphine action of Ca^{++}. These studies were mostly carried out by Harris, Iwamoto, Huidobro-Toro, Hu, Chapman, Schmidt and Rezvani.

The acute lowering of Ca^{++} by opiates initiates a homeostatic response to prevent Ca^{++} loss. This counteradaptive process requires the presence of morphine and becomes increasingly effective with each successive dose of morphine. Yamamoto, Harris, Guerrero-Munoz, and Chao found that the development of tolerance to morphine is accompanied by an accumulation of synaptosomal Ca^{++}. The subcellular components involved in this increase include the inner synaptic plasma membrane and vesicles and the increase in Ca^{++} is proportional to the degree of tolerance developed. Since Ca^{++} antagonized acute morphine action, the accumulated Ca^{++} could oppose opiate effects and more morphine would be required for reducing Ca^{++} to produce analgesia. However, the higher dose of morphine would further enhance the Ca^{++} retention process and render acute lowering of Ca^{++} even more difficult. Thus, a mechanism was provided to explain tolerance.

The proposed cumulative enhancement of Ca^{++} retention by morphine also provides a mechanism to explain cross-tolerance. The elevated Ca^{++} and its increased retention capacity should not only reduce the effects of other opiates but also those of other agents that reduce Ca^{++}. For instance, tolerance to morphine was demonstrated to result in cross-tolerance to La^{+++} and to EGTA.

Physical dependence is an invariable accompaniment of tolerance and the two states appear to be closely linked. Under such conditions cytosol Ca^{++} may be maintained at a higher steady state by the enhanced retention process, which requires the continual presence of morphine. The need for morphine to support this retention process was indicated by the finding that administration of naloxone to precipitate withdrawal results also in a marked fall in synaptosomal Ca^{++}. Abrupt discontinuance of morphine or antagonist-precipitated abstinence results in an increase in cytosol free Ca^{++} at the expense of the retention process and the abstinence syndrome would reflect hyperirritable responses to Ca^{++} that ordinarily are masked by morphine. Hence, when morphine is administered during this state, abstinence would be suppressed because the free Ca^{++} becomes reduced not only by decreased cellular uptake but also by enhanced intraneuronal removal at amplified Ca^{++} storage sites. Consistent with this postulate, maneuvers designed to lower free Ca^{++} suppressed abstinence and elevating it exacerbated the syndrome.

The more recent findings with respect to the effects of the cyclic AMP system on opioid action almost certainly will be meshed with those of Ca^{++}. Ho and Loh alluded to the possible role of cAMP in opioid action in 1972. Current knowledge indicates that opioids initiate their responses via the cyclic AMP system by promoting coupling of the drug-receptor complex to guanine nucleotide regulatory (G) proteins. The involvement of G proteins on the gating of Ca^{++} point to a possible relationship in opioid action. Also, the work on polyphosphoinositides provides a new second messenger system that may link opioids and Ca^{++} effects. I look forward to future work in these directions.

In summary, our approach towards combating the problems of drug dependence has been essentially pharmacologic and directed towards ferreting out the basic mechanisms involved. Although I would without qualification concede that misuse and abuse of chemical substances reflect signs and symptoms of individual and societal maladjustment, the pharmacologic approach provides a knowledge base that facilitates psychologic, psychiatric, and rehabilitative measures.

IDIOSYNCRASIES

Sports and arts have always given me much enjoyment but I would rather be a participant than a spectator. If the role is passive, the greatest pleasure is to

hear an elegantly crafted science story. Usually my attention span is poor but I become enthralled when a brilliant scientist with the ability to sell unfolds an imaginative concept from derived data or provides a lucid and reasonable explanation of unanticipated results. Some memorable lectures were the ones by Szent-Gyorgi on muscle contraction, Bishop on oncogenes, Raftery on the acetylcholine receptors, Eccles or deRobertis on neurotransmission and duVigneaud on the isolation of pituitary neurohormones. Sometimes the discovery can be noteworthy but the story most dull. Many in the audience dozed as Waksman, the discoverer of streptomycin, dutifully plodded through a narration on the screening of zillions of compounds for antibacterial activity.

I enjoy competing in sports. Now it is only golf and coaching my grandsons but it used to be basketball, baseball, table tennis, track and field. A poor loser can be tolerated but not a poor winner. It is very galling should I happen to lose to my colleagues E. "Jack" Cafruny, Ted Brody, or my Chancellor Julie Krevans. Probably, I am no less gracious when I win and they are only reciprocating.

I love popular music. The type is dictated by chronology and enjoyment of ballroom dancing. Nothing is more exhilarating than gliding or stomping in unison on the floor with an accomplished partner to the tunes and rhythm of the big bands. The sweet lyrics and arrangements of the thirties and forties are a far cry from the ear-splitting and perpetual monotonous disco gyrations that so enamor younger generations. Fortunately, the laws of nature have been obeyed and the development of a resistant population has given birth to the revival of touch dancing. Also a new breed of young musicians who can emulate if not revive the likes of Duke Ellington, Glen Miller, Benny Goodman, Les Brown and Xavier Cugat are appearing on the scene.

The dances in the thirties and forties were intensely romantic. We bought our dates corsages and last dances were always accompanied by sentimental lyrics without social messages. Of course, we didn't have to contend with the injustice of the Vietnam war as the flower children did in the sixties. In our times, women had more passive roles and were placed on a pedestal; I still do that. I once was accused of being a chauvinist which I took for a compliment because it was nicely modified to indicate that I was chauvinistic in the right way.

My work has enabled me to travel extensively. I have been to all fifty states of the United States and to many foreign countries, including some behind the iron and bamboo curtains as well as to the Berlin Wall the day after it was erected. The plight of the nationals in these countries made me ever more appreciative of a democracy and the foresight and courage of my parents to emigrate to a land where there is freedom of opportunity and speech.

I believe ardently in a free press, but have often seen it abused so I

adamantly insist that I believe in a *responsible* free press. A good reporter and news analyst can be most enlightening but there are those who fabricate or manipulate the facts to suit the needs for power, glory, or money. I don't know whether journalists have a code of ethics like the health professions but the media certainly could use one or follow it more closely if it exists.

Irresponsible university administrators negotiating huge indirect costs to carry out research always get under my skin. Some institutions want nearly as many dollars as the investigator needs to pursue a research project. Such greed will inevitably kill the goose that lays the egg. In fairness, legislators (under political pressure) constantly impose additional burdens by necessitating conditions for affirmative action, human and animal research, and perhaps soon for misconduct, but there has to be a limit. Why shouldn't indirect costs be subjected to peer review?

Speaking of peer review, the system has often been the subject of much criticism. I remember one instance in particular when I was chairman of a pharmacology study section. A brilliant scientist submitted an application to study the mechanism of opiate tolerance and physical dependence based on concepts of bacterial resistance. After heated debate, his grant was turned down because the hypothesis seemed incredible, preliminary evidence was lacking, and the size of budget was inflated. The minority group argued in vain that the opiate field needed established investigators with fresh ideas. Fortunately, an embryonic National Institute of Drug Abuse, which was then part of NIMH, supported the investigator who subsequently developed the concepts for receptor binding and isolated dynorphin. Of course, such injustice is the exception instead of the rule. Like grades, peer review cannot be perfect and can be improved, but I can't think of a better or fairer method.

REHIREMENT

Retirement became official in 1987 but I managed to hang on two additional years. Mandatory retirement age at UCSF is 70 but since I was only 69 years and 355 days old at the beginning of the new fiscal year I was eligible to stay on for the rest of the year. I was then rehired for another year because the University had committed to support my grant beyond my retirement age. However, all good things come to an end. My friends honored me with a symposium and a lavish champagne party at the Fall (ASPEC) Pharmacology meeting in Honolulu which I shall always remember.

My luck still prevailed. Also attending was an old and dear friend, Eikichi Hosoya. He asked me to help set up a new department at Gunma University in Maebashi, Japan, and so in 1989 I became the first Tsumura Professor of Neuropsychopharmacology. The language barrier and the cultural gaps presented some problems but nothing compared to the frustrations imposed by

the bureaucracy, which the Japanese manage to tolerate and endure. In my own mind, I did not accomplish much on the job because many things had been or were being done without me. Other than delivering a few lectures, giving unheeded advice, and correcting some research papers, I was pretty much on my own and was allowed to go abroad to attend scientific meetings. On the other hand, the pay and perks were very good. I learned a lot about Japan and made some very good friends. Most impressive is the respect and devotion the students give professors and I was deeply touched by the treatment accorded me by my former associates. The new breed of young scientists are skilled and innovative.

On returning to the United States in 1990 I accepted an invitation from Bob Schuster, Director of the National Institute on Drug Abuse, to become a consultant and was given the title, Senior Fellow. It was a great learning experience. By and large government employees at the professional level are highly capable, suffer through the vagaries and inconsistencies of government, and work long, hard hours to get the job done. They have to maintain a broad perspective and much patience dealing with the public, the legislature, and other government agencies. My respect for them has been enhanced manyfold. As for my own contributions, I'm not certain about their value. I might have enhanced the role of clinical pharmacists by calling attention to their potential usefulness in treatment and research programs. I directed more attention to drug problems among Asians whose problems are steadily mounting as the numbers and types of immigrants increase. I also indicated that we might learn from institutions using nondrug intervention methods to rehabilitate addicts, such as the highly successful Delancey Street Foundation in San Francisco with self-built quarters as posh as any deluxe hotel. My government services terminated this year by mutual agreement. I might have stayed longer but I have a very challenging opportunity that should keep me occupied for another two or three years.

Professor Joseph Needham of Cambridge University invited me to write the volume on Pharmacy and Pharmacology in his series *Science and Civilization in China*. Needham, considered to be the world's foremost scholar of Chinese science, has been writing on the subject for over half a century. In his seventeen published volumes, he points out that many uncredited discoveries and others attributed to the West, were actually Chinese innovations. Moreover, the contributions helped immeasurably the agricultural and industrial revolution in Europe. Francis Bacon opined that the mariner's compass, paper, and gun powder had a tremendous impact in transforming the world from a feudal to a modern state but he died without knowing that the inventions were Chinese in origin. There are also many other innovations that are in everyday use such as the umbrella, parachute, wheelbarrow, fishing reel, iron plow, and porcelain dishware.

Relevant to my own task, what a revelation it has been to learn about early bioscience in China. Circulation of the blood was described more than two thousand years ago; sex hormones were isolated from urine by sublimation and small pox vaccination was used for over one thousand years; goiter was treated with sea weed and animal thyroid glands for at least one half a century. It is my intent to find out how the Chinese contributions facilitated the emergence of pharmacy and pharmacology as disciplines. In the ancient writings, there are discussions on drug interactions, drug-host relationships, neonatal pharmacology and how conditioning and environmental factors can alter drug action. It is a formidable and exciting undertaking to tackle. To help me in my tasks, I shall collaborate with Professor Chen-Yuan Lee and a former student Yong Qing Liu.

My letter-writing over the years can be severely faulted so I'm trying to atone. I am grateful to the editors for giving me the opportunity to catch up with my correspondence.