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OUTLINES OF A PHARMACOLOGICAL CAREER

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I must preface my notes with an honest declaration. No doubt my acceptance of the friendly invitation of the *Annual Review's* Editorial Board to write a prefatory chapter was rather inconsiderate, and I was long meditating how to discharge my obligation. For, during the preparation, I became aware that this kind of literary pursuit was for me not only new but a venture. The primary enthusiasm turned into hesitation. Two considerations helped to overcome my indecision. First, I learned that a meditative reconstruction of the sum of the inside and outside events of one's life is a personal benefit and that growing older poses a rather personal need to hold audience with oneself. But I found that analysing and portraying somebody else is easier than portraying oneself. On the one hand, the portrait should be honest and realistic so as to be recognized by the friends and colleagues with whom I passed the time. On the other hand, the historical reminiscence has to be constructive enough to interest colleagues of the younger generation. Despite, or perhaps because of, the breathless speed of progress in any field of natural science or medicine, there is, interestingly enough, a general trend toward a historical view or concern. This I hope may favour interest in the historical adventures of the prefatory chapter.

So I see my task dual in purpose and result. The following discourse is a potpourri. The main melodies will be: Who is he; Why, Where and What did he do; as well as, How does he view the development and future of pharmacology? In so writing the prefatory chapter, I wanted my friends and colleagues to know more of my early progress. The description of it means a contribution of the history of pharmacology, the individual part of the whole. History is not merely a record of the past but also the relationship of the past to the present situation. It is a truly continuous development and the course of its problems is its history.

In committing some thoughts and events of my career to paper, I hope to show the younger generation the course of pharmacology during the last 50 years as I experienced it. Depicting this cross section of my life, I shall follow the admonitory device of Voltaire: "Le secret d'ennuyer est celui de tout dire."

Although I believe that I hardly belong to the few individuals whose particular personal talent and performance makes them qualified subjects for a biographic record, nevertheless, I will endeavour in the following pages to discharge my obligation. The prospective reader is invited not to expect more than I can offer.

I was born and brought up in Lachen which means "marsh" and not "laughter"—on the lake of Zürich in a marvelous landscape of fruitful plain with mountains in the background and a view of the Alps. It is about a half

day's walk from the birth place of Paracelsus. I had three sisters and two brothers. My father was industrious and persevering, rather guarded and reflective; while my mother was indulgent and very open-minded, imaginative, and enterprising. From them we learned honesty and responsibility, love for nature and even for music which they did not practice. In accord with his different talents, my older brother was sent to a commercial school to become the successor of my father in his thriving business. I was sprightly, an easy learner, with an active interest in anything new. I used to play the violin for two hours before breakfast in order to enjoy leisure after school with my school friends. My parents decided to send me, after six years of primary school, to a high school. But because of a serious hepatitis, called icterus then, that was postponed for a year.

Here is a story which seems much to the point in this context. When I informed my music teacher that I was leaving for the high school, he came to see my parents, insisting that I should become a musician. The answer was precise and definite: "we like music very much as an entertainment but not as a profession." I not only agreed but was most astonished about the praise by my music master, because he was ordinarily rude to me despite my usually performing my theme by heart. Violin and singing—I never could yodel—were my hobbies and were practised until professional work occupied all my time.

So I entered the "humanistic gymnasium" of a clerical college. There was no difficulty at all in learning. But the internment did not correspond to my kind of gregarious inclination and home education. I could not adapt to such a narrow-minded, restrictive form of mass education. After three years, another attempt as a day student in a similar clerical college was not a success either. Being an ardent botanist and climber, I saw no harm in stepping over the allowed geographic borders or in dancing during carnival. Twice reprimanded, I was finally expelled and that for a glass of beer! The director of the college insisted on a demonstration, contrary to the advice of all my teachers. He had the queer idea that it should be in the church, in the presence of the whole community. The psychological effect that this behaviour had on me needs little explanation.

The event was, of course, an impressive personal shock. But the consequences finally turned out for the best. First, my greatest satisfaction was that my parents understood psychological education and also youthful escapades. They did not withdraw their confidence in their son. I confessed with all frankness what had happened and that my behaviour was incorrect, but I demonstrated that cause and result were not in proportion. They did not palliate my behaviour but considered it neither scandalous nor indecent, and so, pardonable. After repeated discussion, the director remained wroth. No presentation of the facts was accepted. He even refused to grant a certificate of my school accomplishment, and because that was urgently needed for my acceptance in another school, I saw my way barred. This outcome was the autocratic decision of the director alone, for all my teachers were sympathetic, though the monastic rules did not allow any intervention. Fortunately

for my colleagues, this director himself was dismissed about a year later. No explanation for this event seems needed!

Meanwhile, I had a chance to enter the cantonal gymnasium, St. Gallen. The director was informed about my case. He asked for my certificate and got it, and I was welcomed without passing an examination. This proves that the programme of my former school was adequate. Now I felt at home in every respect, in the natural pleasant atmosphere of the school and in familiar lodgings and social life. I got my "matura"—license permitting entrance to a university—in one and a half years instead of two. It was hard work, but I liked it.

While I had failed to find real friendship in the hypocritical climate of the former six years, here I easily made lasting friends. Also, I was able to harmonize school duty with leisure attractions such as visiting the art museums, theaters, concerts, sport and even dancing. The core for this happy feeling was the mutual help between the pupils, as well as the friendly, respectful, and unauthoritarian relationship between pupils and teachers. This was an excellent preparation for free university life emphasizing self-discipline and self-responsibility, the two main qualities I had been taught at home. By and large, I felt myself a free conscientious member of a lovable human community for the first time. During this period I found it necessary to answer the questions, Who am I? and, Where do I come from? I overcame this decisive period thanks to the understanding and confidence of my parents in the lively, self-willed and independent, but not obstinate, character of their son. This experience recalls the report delivered in 1942 in Basle by Julian Huxley, who said that the milieu a child is brought up in during his first years determines whether he will become an honest member of human society or a good-for-nothing.

However, the tale would be incomplete if I passed over a delicate point, i.e., the psychological effect that the form of my discharge—to be thrown out of the church—had on my belief in various dogmas of Catholic confession. My family was Catholic but by no means orthodox. Contact with natural science and some books which were on the *Index Librorum Prohibitorum* had raised doubts that were reinforced by this event. A disturbing imbalance and remorse preoccupied me for some years. It was a problem I had to solve myself. Books on general and natural philosophy were read, but I found the final solution in reading the golden book of nature during my walks. I became a follower of the ecumenic movement and founded a family with a Protestant wife. We harmonized marvelously and had two children of whom we did our best to make good Christians.

The first and primary landmark was passed, and I entered the medical school in Geneva full of hopes for the highly regarded possibilities of university life. If I have one objection to the high school programme in St. Gallen, it is the unbelievable lack of help and guidance for the university's newcomers by its teachers, and the lack of guidance appropriate to individual talent. I do not mention this because of my own case but for that of hesitant comrades.

Genealogically I am descended from farmers, artisans, or business people but have no ancestors in science. Though multiply gifted, I was fascinated by natural sciences and decided to become a chemist. This was vetoed by my father who said: "I know what a physician is, but I do not know what a chemist is good for." I went with enthusiasm into medical training but with the reservation that I would later study chemistry at my convenience. I entered the French-speaking medical school in Geneva full of scientific and cultural expectations. It turned out that our high school preparation in French enabled me to follow the lectures easily. Yet I was unable to listen and write what I heard at the same time, i.e., to keep a "book of lectures." I censure this system, still practised, as antiquated and nonsensical, since it hinders attention and understanding. Besides, there are excellent books for information, while a "lecture book" is always incomplete and often erroneous. Moreover, I am convinced not only that my system is time-saving but that it sharpened my memory, which became my most faithful friend.

In this first year, I had the luck to hear two splendid teachers, Pictet in chemistry and Chodat in botany. Pictet excelled in clearness and elegance, Chodat, in impressive eloquency and stimulation. His introduction to general biology was my first contact with the basic problems of life, its origin, evolutionary development, and problems. We became aware of the scientific importance of the genetic rules of G. Mendel for biology and medicine, published in 1865, and rediscovered in 1900 by DeVries, Correns, and Tschermak. This opened our eyes to the steady increments of natural philosophy: Lamarckism versus Darwinism, materialism versus vitalism, and so on.

The year ended well with an oral examination in physics, chemistry, zoology, and botany. I got a prize, not from the university, but from my parents, consisting of an extra monthly allowance. I spent it with a friend for a most enjoyable trip visiting the principal cities of North Italy. What a remarkable revelation in all facets—artistic, social, and culinary, and in natural history.

The next one and one-half years were devoted to anatomy, histology, embryology, and physiology. I think the anatomist, Laskowsky, was the best teacher I ever had, a real animator with modern concepts, arranging seminars where students had to speak and discuss, and all in a most friendly atmosphere. Physiology, my preferred branch, was given by the famous J. H. Prévost, unfortunately at the end of his career. When examined on the function of the vagus, I also mentioned that of afferent nerve fibres, disagreeing with the book. Unwilling to accept the word of the book, I insisted on proposing a verification of the book, which was refused, and I received a bad qualification. This behaviour was typical of some examiners and also of me! But this could not disturb the unforgettable experience I had in Geneva.

The entrance to clinics is rather an emotional event. It should be real contact with patients, but it was then and still is now just a demonstration in an amphitheater where the professor lectures profoundly on a case before 100 to 1000 students. It is, doubtless, a system which should have been abandoned long since. Gradually it will be changed. This is necessary not only for

educational reasons but because the student would like to learn whether practical medicine corresponds with his mental picture of a physician. After my favourable experience in changing high schools, I was eager to become familiar with another culture and decided to go to Berlin, at that time the dream of all German professors in medicine. The choice was enormous. Each discipline was presented several times. After looking around for a month, I fixed my plan. According to my preference of pathophysiology, I frequented daily, from 9 to 2, the lectures in internal medicine with the brilliant Kraus, extremely well versed in pathophysiology. This sober but systematic searcher, and Goldscheiter, the most skilled policlinician, collaborated in diagnostic exercises on patients.

This profound training in internal medicine was a lasting background in the anamnestic, diagnostic, pathophysiological, and cathamnestic viewpoint. Particularly attractive for me was Hefter's pharmacology, not for his eloquence but for his skilled experiments, assisted by Joachimoglu, later professor in Athens. The third partner, Lewis, a famous toxicologist, fascinated us by his tales of the adventurous role that many drugs played in old and new culture periods. The winter of 1911-12 was so harsh that our urge to visit the pleasant environs was at zero.

We—always with my studymates from school—took advantage of all the cultural possibilities the very lively Berlin offered, so far as our purses allowed. Berlin was not a pretty town, but for its activity, very stimulating with an amiable and witty population.

How different were my later visits to Berlin: in 1923, the postwar depression; in 1937, Hitler's disastrous move; and in 1949, bombed and separated in West and East. The latest visit was to redeem a promise given to the late Heubner that I would visit him as soon as he would change over from the Humboldt (East) to the Free University (West). I argued that West Berlin with one and one-half million inhabitants, without the scientific, cultural, and social irradiation of a flourishing university, was inconceivable for me.

For a week I lectured and discussed this before a stimulating audience. It happened that the late Oberbürgermeister, Reuter, a most courageous and remarkable personality, initiator and founder of this university, thanked me. Our contact lasted until his too early death.

I spent another term in Kiel, more as a recreational compensation for the heavy work in Berlin than for study. The main attractions were the huge navy harbour, the fine opportunity for sailing, and riding horses during the week, at very low cost, as they were usually ridden only by Sunday riders.

I shall never forget the ambiguous impression provoked in us peaceful democratic citizens by the formidable navy parade, attended by the emperor—the provocative hip hip hurrah, the emotion of mass psychosis with tears. It was too bad: a prognostic sign of the coming critical upheaval.

News of the bad health of my father called me back before the end of the term. Unfortunately, the young student had to correct the diagnosis of the elderly doctor; X rays confirmed cancer of the stomach. From prolonged anaesthesia and careless aftertreatment, the operation was not a success.

For the last three terms, I was in Zürich. Two teachers held particular attraction for me: Bleuler, who taught the psychological introduction to psychiatry, and Cloetta who taught pharmacology in a very wise and superior manner, but deplorably, without experiments or practical exercises. This is still a serious lack in the Swiss medical programme.

After an examination lasting three to four months, and certification as a physician, my pleasant and instructive life as a student came to its end in June, 1914. What now? First, some reflections on our medical program, and the relation between professor and student. The programme consists in too much professorial teaching and completely passive behaviour of the student. The analogy of "fattening geese" describes the situation. The level of active mental collaboration and the stimulation of critical thinking is lower than in good high schools. The worst of all is the complete lack of coordination of subject matter. Each institute or clinic has its own programme, and the integration of the parts remains the difficult task of the student. The medical training is too theoretical, since little or no occasion is offered for discussion or practical application of acquired knowledge; and this means little contact between teacher and student. Some of us, feeling this lack, volunteered spontaneously to serve in hospitals during the holidays. The practical contact with patients is so poor that the physician with a Federal diploma feels it necessary to continue his education for another six to seven years. This is why the quality of Swiss physicians is better than would be presumed from the official programme of medical training. The situation is going to be changed; I only hope not too slowly and timidly. The situation for a scientifically interested and qualified student was even less favorable. The medical training gave no chance for real contact with the teacher. The latter seemed neither interested nor concerned in the training of the a younger scientific generation. There were no grants and no fellowships, only one's own initiative. Since biochemistry was only in embryological state, I decided on pharmacology. I went to Cloetta and asked for an assistant's post, but the only one was occupied by a German chemist. He advised me to study organic chemistry until the place became free, but it never became free for me.

Before I left for Geneva to be trained in organic chemistry in Pictet's laboratory, the war broke out. I had to replace an assistant in internal medicine, which post allowed me to do my thesis on the "Reaction of Abderhalden." The current hypothesis was that the appearance of "protective enzymes" in blood was due to the entry of proteins into blood during pregnancy (from the placenta) or pathological processes in other organs. This first experimental approach was in any case an exciting and instructive challenge. My clinical duty in the dermato-venerological wards—at that time included in internal medicine—allowed me to do experimental work, and the laboratory was open day and night. From this first experimental experience, I learned that the solution of a hypothesis needs not only planning and design but a corresponding knowledge of the processes involved and reliable techniques. Another acquisition was that experimental research must state objectively and honestly whether the results confirmed the hypothesis or not, instead of adapting

the results, consciously or unconsciously, to the hypothesis one would like to see established. Such discrepancies provoked my independent thinking, and sharpened the sense of objective observation in my own work as well as in that of others. The short clinical experience excited my imagination inasmuch as I was astonished at the defective and unsatisfactory state of our basic knowledge of diagnostics—functional and biochemical—and of therapeutics. One of my unforgettable experiences was that with “old” Salvarsan that I was asked to reintroduce despite some previous serious side effects. The drug proved effective, but even the most cautious intravenous infusion of 500 cc of the alkaline solution induced venous thrombosis regularly in the patients and sleepless nights in me.

My thesis ready and accepted, and an assistant-substitute found, I would have been free to leave the clinic and realize my intention to join Prof. Gley, the endocrinologist, in Paris, except for the war. No place in physiology or pharmacology was free. I decided to enter as a volunteer, the laboratory of organic chemistry of Prof. Pictet and so to fulfill my primary desire, and to complete my preparation for pharmacology. Following the standard “Kochbuch” by Gattermann, I did most of these prototypes of organic synthesis, enjoying the pleasure of crystallizations and correct elementary analyses. With Kaufmann the synthesis of damascenine, a natural perfume from the seeds of *Nigella damascena*, was successful, as was collaboration in a step of quinine synthesis.

Pictet encouraged me to take the examination for the Ph.D., accepting one of my papers as a thesis, but the demand of the professor of inorganic chemistry to spend one year in inorganic analysis did not appeal to me. As the prospective post with Cloetta was still occupied, I accepted an offer to join Prof. Battelli, head of the Physiological Institute in Geneva, as a second assistant. Lina Stern, later professor in Moscow, was first assistant and active in research, while Battelli was mostly preparing his daily lecture. This was most critical theoretically and historically and so elaborate that I still regret that he did not publish it as a book. For me it was an easy way to get acquainted with old and current literature on one hand, and with research on the other.

Battelli entrusted me with testing the hypothesis, promoted by Pagano, that the center of emotion is localized in the cerebellum. He had found that injection of curare into the vermis in dogs elicits a picture of excitation and emotion followed by clonic and tonic convulsions and finally by death. My job was the experimental part. The findings were that injection into the cerebellum or brain of even 0.1–0.2 cc of a dye solution showed the fluid spreading back and forth. The application of 1–2 mg of crude curare fixed with gum arabic and placed with the mandrin of an injection needle at various places in the cerebellum elicited only known motor effects. But, as a case of serendipity, it happened that the needle pierced the cerebellum and the point entered the fourth ventricle. Now the picture described by Pagano appeared: curare given into the third or fourth ventricle in dogs, cats, rabbits, or guinea pigs provoked the “Pagano syndrome” while that into the

cerebellum had no effect. About 40 years later Feldberg and Sherwood confirmed and developed these important findings.

The high activity of this raw curare intrigued me. I purified a very small amount and demonstrated an extremely active compound to Battelli. Here was a great chance to isolate and define the active principle as there was about 500 g of active curare in stock. Unfortunately, Battelli would not let me have the precious curare.

Another extensive study in collaboration with Stern was the physiological and chemical characterization of extracts of liver, lung, and spleen, using isolated uterus, intestine, and blood vessels as indicators. The spleen proved to be the most promising. While the constrictive activity of fresh and purified extracts of the spleen corresponded rather well with that of histamine, chemical behavior of the purified extract was in opposition to this concept. We called the active substance provisionally "Lienine."

Hardly a year after my entrance into this incomplete work with curare and lienine, the chemical characterization came to an abrupt end. In Zürich, Gaule, the professor of physiology, had to retire because of illness, and Hess was appointed as interim substitute. He badly needed help in administration and lecturing; Cloetta recommended me to Hess, who asked me to join him as his assistant. All the posts, the head, assistant, technician, and servants (the latter responsible for the care of the animals), were provisory until the definite nomination of the new professor, which Hess hoped and deserved to be. The various pros and cons for staying in Geneva or moving to Zürich were considered. Why did I choose Zürich?

The atmosphere in the institute was rather heavy, mostly because of Battelli and Stern. Battelli was a most cultured personality for whom I retain a great reverence. He was a very skillful and hard worker. I shall never forget the brilliant demonstration, as a result of his work with Prévost, at the conclusion of one of our discussions. A dog was electrocuted, the death confirmed, and then after 5–10 minutes the chest was opened and gentle massage of the heart and of the peripheral blood towards the heart made fibrillation start. An intravenous injection of BaCl_2 was given, and following a galvanic shock, normal heart rhythm appeared immediately. The chest was closed, the dog awakened and moved around. It was a wonderful event and suggested many problems. Battelli was always correct and accessible and concerned in discussing problems he was interested in. However, discussion on my prospects started well but turned out badly: it was not worthwhile to begin with curare, the general outlook for the future was not hopeful at all; a separation of physiology and biochemistry was an untimely dream of the younger generation. Lastly, the income was that of a gratuity, though I was still prepared to make use of the modest gift my father had left me for my education. The risk in Zürich was that if not Hess, but the German competitor, were nominated, he could bring his staff with him, and I would probably be "free." The German influence was strong not only among the German but also among the Swiss members of the faculty. It may be noted that Hess would be the first Swiss physiologist in the German-speaking part of Switzerland. Fortunately,

he was elected. He was not only an excellent teacher for students and post-graduates and an original and outstanding researcher, but later a Nobel prize laureate. He founded successfully a school of Swiss physiologists and a new mind and trend in the younger generation of Swiss scientists who saw a more favorable future in academic competition, not only in physiology but in other branches of medicine.

After this deliberate and discriminating detour, I come back to my dilemma. At once Hess impressed me by his straightforward behavior, his frank and logical reasoning, and by his enthusiasm for the great task he saw before him. The prospective income would cover the expenses of a modest scientific celibate liking books, theater, music, and some participation in sports. Nevertheless, the farewell from Geneva after six years there was hard, and only the fine memories of this exciting and pleasant town with its remarkable environment made it easier.

My first contact with Hess was a long conversation outlining a clear-cut schedule of lectures and practical exercises for students, and then personal research. Hess's concept of teaching was a sympathetic new look, inasmuch as demonstrations were customary. The student had to understand physiology by passive and active experience, and even from unsuccessful experiments which had to be repeated the next day.

I remember the demonstration of hibernation and its mechanism. A hedgehog well-nested in a box in a cool room waited for the spring. About the end of the term, I brought the mysterious box cautiously to the lecture table. Hess unpacked it with care and made a subcutaneous injection of a pituitary extract, but nothing happened. Before the next day's demonstration, I put my nose near to the animal, and the smell stated death, confirmed by Hess.

My training in lecture-experiments and the preparation and carrying out of the practical exercises left practically no time for research. However, this was a most instructive postgraduate course in physiological techniques for me. In addition there was great tension. This term was by way of a test for Hess's nomination in which his ability was surveyed by members of the faculty and the government. Therefore, there was wholesome relaxation for us all when Hess was definitely nominated. Daring a comparison between the climate in Zürich and Geneva, I would say at Zürich there was the young, spontaneous, open-minded original searcher full of systematic and decisive drive, discussing all administrative, educational, and scientific problems with his staff. At Geneva there was a wise, experienced scholar, mostly meditating after a very active life, interested not only in scientific matters, but in political, social, and artistic concerns.

Soon Fleisch joined us and so two backs were bearing the duties of assistant, facilitating personal research. But scarcity of money limited our expansive drive. With a small budget, and no grants or fellowships, the chief and his two assistants depended on one technician. Our motto was help yourself and do it yourself. The experience in manual ability acquired in my provincial boyhood, visiting and helping any kind of craftsman, was welcome. Fleisch was a city boy and had a particular manual skill in making scientific

apparatus. This, he told me, was his Sunday hobby. I thought to compensate for the scarcity of time for research by night work, but this was not allowed. I mounted my apparatus for viscosimetric studies in my living room. This technique was suitable for such arrangements. It was a problem which Hess was promoting and for me was an excellent way to become acquainted with the current problems of colloidal chemistry so much in vogue at the time, and so important for the understanding of biological processes.

Enzyme studies followed, and I got involved in a controversy. Biedermann maintained that even ashes of saliva induced enzyme activity. Our results were negative when strictly aseptic, confirming the gossip I learned from a colleague that the positive results were due to wet contamination.

With time we succeeded in interesting capable students in research and in studies of long duration. I am indebted to Gundlach, a skillful, confident, and trustworthy student, for enabling me to perform the study of the influence of histamine on stomach secretion in the Pavlov dog's pouch. Unfortunately, Gundlach, a keen climber, had to pay his tribute to this national sport very much too early. Working independently and starting from quite different considerations, Popielsky also published the stimulating effect of histamine in 1920. Our analysis considered not only the amount of secretion, but also the general and enzymatic

intravenous, and negative effect after subcutaneous, injection. A clinical application seemed reasonable. The people in the medical clinic being reluctant, asked Cloetta for advice. He said that histamine was a dangerous agent. Too small a dose was tried, so that the clinical result was not relevant. The proof of its clinical value was reserved to less hesitant people. This is an example of Paracelsus' rule, stating, "Any substance is toxic; it depends on the amount whether it will be a useful drug," which was not then commonplace.

Also I kept in mind to continue the work on "lienine" and other organ extracts, which I looked upon as interesting and relevant, and because my scientific trend aimed at biochemistry. Wirth and I were able to demonstrate that the effects of purified extracts on isolated organs, such as heart, vessels, uterus, and intestine, were identical with those of choline. However, the following observations were inconsistent with this concept, in that a cooled fresh extract was more active than one prepared at room temperature or heated; addition of acetic acid prolonged activity; alkalization of the acid extract decreased activity very quickly and strongly; and atropine blocked the action. The final chemical purification by different steps led to a crystalline platinate salt of a very high activity, identical to the fresh acid extract. The remaining amount allowed only one microanalysis which unfortunately was not successful. The extremely high activity and the chemical and biological behaviour of this substance of the spleen pointed to the presence of choline ester. All was prepared for a repetition with an amount of spleen as great as the limited facilities permitted. This promising endeavor was abruptly cancelled when Professor A. Stoll, head of the recently established pharmaceutical department of the Sandoz Ltd., offered me a place as pharmacologist, on the advice of Cloetta. I found myself in a dilemma. The spontaneous

reaction was to say "no". After my training and education in physiology my preference was biochemistry. My interest in the stirring findings on amino acids and proteins by E. Fischer was occasioned by a stay with Plimmer at the Rowett Institute in Aberdeen, working on amino acids. The contact with English colleagues and literature enlarged my insight into the enormous possibilities regarding enzymology, endocrinology, and vitamins. In 1920 I got the first degree, i.e., "privat docent," of an academic career which has its adventure, too. Hess and I attended in 1920 the International Congress of Physiology in Paris, my first, and unforgettable, congress experience. Before the end of the Congress, a cable from the Dean called me back to give my trial lecture before the faculty. It was very characteristic that Hess decided to leave the Congress prematurely to accompany me and be present at the decision of the faculty. Because of a change of the time table, unknown to most passengers, we missed the direct rapid Paris-Basle train. A slow night-train brought us to Vesoul; a taxi to Mulhouse where we had breakfast on a bright morning, and we arrived in Zürich just having time for a shower. I passed, but Hess told me that his colleagues were astonished by my unusually tedious delivery. Hess's information about our adventure cleared it up. The decision of whether or not to accept the industrial position required a lot of consideration. On the one hand, the abandonment of the aim of an academic career with its advantages in respect to personal freedom and scientific independence was the critical point for a fervent defender of Paracelsus' motto: "*Alterius non sit qui suus esse potest.*" Next was the regret for the loss of the cheerful and refreshing contact with students, and an uneasiness at being put into hierarchic machinery. Moreover I would have to give up my current work and plans for the future. Last, but not least, I was indeed sympathetic with pharmacology but had never seen or worked in such a laboratory. How should I find my way being engaged in research I had not conceived? On the other hand, I was offered the opportunity to build up a department, to plan and design my work naturally in prospect of therapeutic application, since success would support the whole pharmaceutical department besides the expectation of the shareholders. The most attractive factor was the collaboration with the skilled and competent Prof. A. Stoll, whose scientific training with Willstätter was some guarantee. The final decision depended on two circumstances: the first was the bleak academic prospect. While encouraging my biochemical leaning, Hess declared that biochemistry would not be an independent department for 15 years, and so it happened. Then the German biochemist, Flaschenträger, got the chair but, being a Nazi, had to leave after the war. The second attractive factor was that the faculty of Basle had accepted me as "privat docent," i.e., allowed me to give lectures, and Sandoz approved it, too. To be frank, I also found it advisable at 34 years to have a post with a marriage income.

On the first of April, 1922 I motored with my dog in the sidecar to Basle. My predecessor, K. Spiro, appointed successor to the biochemist, Bunge, had left an empty office and three working rooms in an old shabby building containing a few instruments and some apparatus. In great contrast, three chemi-

cally defined substances, ergotamine, scillaren A, and bellafoline, isolated by Stoll and co-workers, were waiting to be investigated. There was enough work for a team of pharmacologists. Now I found that pharmacology was an interesting part of physiology, then using nearly exclusively physiological techniques familiar to me. Consequently, it was for me not an "occupation of those who deal with physiological problems without troubling to acquire the technique," as Sir Henry Dale said, defining pharmacology. In this primitive ambient were an excellent mechanic, two technicians, and a secretary who all were eager to learn and help and were involved part-time in experimentation. I have always said that it is not the cage, but the bird in it that counts.

It is neither the scope nor the purpose of this report to review known—and if not known, certainly rediscovered—data, but to present mainly some raisins of the pie, some facts and adventures occasioning a glance behind the official scenery. The ergot problem followed me like a shadow for nearly 40 years and its development turned out unexpectedly. I will consider it in three periods.

According to the current trend, skilled organic chemists paid increasing attention to isolating genuine substances from plants and animals either for scientific interest, or for therapeutic application. To a certain extent I was involved in a contradictory situation produced by two prevailing questions: (a) Were the biogenic amines or the alkaloids the specific substances of ergot? (b) Were there chemical and pharmaco-therapeutic differences between the various alkaloids worthy of notice?

The first question was settled soon in the experimental and therapeutic agreement that the biogenic amines, though found in many extracts of plants and animals, were without effect in obstetrics after oral administration, and were not responsible for this particular activity of ergot.

The clarification of the second question was more complex in nature and prestige. In short, the chemical aspect dealt with the delicate topic of whether ergotoxine, isolated by Barger and Carr in 1907, and ergotamine, isolated by Stoll in 1918, were different alkaloids of ergot. My results with ergotoxine from different sources varied to such a degree that I questioned its homogeneity. Any doubt about a chemical difference between ergotoxine and ergotamine was excluded when Stoll and Burckhardt established that ergotoxine was a variable complex of ergocristine, ergocornine, and ergokryptine, while ergotamine was a unity, though able to form a complex with ergotamine. Pharmacologically, Dale (1905–1909), in outstanding studies with impure chrysotoxine and ergotoxine, arrived at two fundamental conclusions: there was a primary stimulant effect on plain-muscular organs, arteries, uterus, sphincter of the iris; and there was a secondary selective paralysis of the augmentor effects of sympathetic nerve impulses and adrenaline. Investigating ergotamine I found similar effects, but with a striking difference. With ergotamine, adrenaline reversal succeeded in cats and dogs in usual urethane morphine narcosis, while with ergotoxine, it was necessary to pith the brain and medulla oblongata, and cut the vagi, and use artificial respiration to study the effect on the respiratory and circulatory centers. The logical

conclusion that ergotamine was one quarter to one third as toxic as ergotoxine or its components, was proven in various species. And what was more important, its lower central toxicity enabled the study of prominent central effects. Thus a thorough comparative differentiation of the five alkaloids by my collaborators brought the following conclusions: 1. The effect of ergot alkaloids was qualitatively similar, but they showed quite distinguishable quantitative differences in the rank of 1:4 according to the test used; 2. The order of sensitivity of the affected functions and of the duration of action was: (a) *central effects*, such as general sedation, potentiation of sedatives and hypnotics, inhibition of vascular reflexes (depressor and carotid sinus), bradycardia; (b) *adreno-sympathicolytic effects*, predominantly the augmentor effects of sympathetic nervous and adrenaline impulses (with the exception of the heart) and in a lesser degree the inhibiting effects of adrenaline (intestine); (c) *constricting effects on plain-muscular organs*: arteries, uterus, etc.

- This statement was a fortunate completion of the fundamental findings by Dale. So I took it as an affirmation, and with a sign of pleasure when Dale, in a dinner speech at the Royal Society of Medicine, said to me, "You started by trying to untangle the active substances of organ extracts especially of the spleen, left it, and continued with the ergot alkaloids, and I went the opposite way."

In my position I was concerned with the two special aims of pharmacology, i.e. (a) to elucidate the influence of drugs on physiological functions and (b) to meditate on the therapeutic application, on the basis of the data gathered, as shown above for ergot. Until 1925, ergot and the isolated alkaloids had one clear-cut indication in obstetrics and gynecology—to induce contraction of the uterus. Ergotamine was successful, as was ergonovine, a water-soluble alkaloid isolated in the same year, 1935, independently by four different groups. The two other effects of ergotamine, the central and the sympatholytic effects, seemed to me to have more interesting and promising prospects. The role of the autonomic nervous system came increasingly under study after essential information was contributed by Gaskel, Langley, Cannon, Karplus and Kreidel, Eppinger and Hess, and Bergmann.

The outcome of my deliberations was twofold. The first result was the treatment of migraine. Since Claude Bernard supposed this to be a state of sympathicotonia, I decided to treat two cases of intractable migraine by subcutaneous injection of ergotamine. Although the theoretical assumption was probably not correct, the experiment proved successful. My friend Maier took up clinical trials and found the treatment effective. After his publication in 1926, the use of ergotamine for migraine became common, and it is still used today, either alone or in combination with caffeine.

The second result was a more complex attempt, namely, treatment of the alleged autonomic dysfunctions of psychic and somatic disturbances supposed to be due to troubled interrelationship of central regulation and peripheral functioning of the autonomic nervous system. Today one speaks about psychosomatic troubles. The combination of phenobarbital, hyoscine (bellafoline), and ergotamine was conceived and an experimental and clinical study

lasting a year, followed. The potentiating effect of ergotamine upon phenobarbital, a new finding, was responsible for the low dose of each component. To make the story short, Bellergal, introduced in 1934, was a therapeutic success. Retrospectively, it is amazing to learn that this combination acted as a central sedative, showing antagonistic effects against the main synaptic transmitters, adrenaline, acetylcholine, and 5-hydroxytryptamine. In a sense it was a forerunner of modern psychoactive drugs, with which it still competes nicely.

The development of these new indications for ergotamine and its combination justified the planning of new, spacious laboratories with adequate equipment. It was also an encouraging example for younger colleagues as to how satisfying the final results of a pharmacological study of a drug could be when the problem was developed systematically according to the two special aims of pharmacology, i.e., physiological elucidation of an agent's effects, and adequate therapeutic application of these findings.

The transformation of the natural alkaloids into dihydrated forms by Stoll and Hofmann introduced the second ergot period. This minute chemical change had big consequences, both quantitatively and qualitatively. The outstanding findings were: very much lowered toxicity, increase of adrenolysis, loss of uterus activity, and competitive inhibition of the muscle contracting effect of the natural alkaloids. Analysis of the striking observation that all dihydrated compounds strongly depressed blood pressure in anaesthetized animals, while in spinal animals the pressure rose, led to the conclusion that the point of attack was central. This fact was the motivation for the therapeutic application of the three dihydrated components of ergotoxine, Hydergine, in essential hypertension and other circulatory troubles. Thus the components of ergotoxine became a useful aid in therapeutics about 40 years after its isolation by Barger and Carr.

The third period was initiated by the successful synthesis by Stoll and Hofmann of new derivatives of *d*-lysergic acid, the essential component of all natural ergot alkaloids. Of the abundant series, too great for close analysis, *d*-lysergic acid diethylamide (LSD-25) found an unforeseen theoretical resonance and a still debatable therapeutic application for its particular psychic effects discovered by Hofmann. Without particularizing known details, I must mention my surprise while lecturing on LSD-25 in London when the audience broke out in friendly laughter at my spelling of the abbreviation L.S.D. (pounds, shillings, pence).

A fourth period of ergot began when Hofmann et al. succeeded (1963) in synthesizing ergotamine, a long-attempted aim of famous chemists. This meant opening new ways for substitution of amino acids in the tripeptide as well as in the lysergic acid component, promising work for another generation.

Less exciting though interesting was the subject of cardiac glycosides, the second major topic of our efforts. The particular purpose for which Stoll and his co-workers had placed an abundant number of chemically defined compounds at our disposal was a differential analysis of their toxicological and

pharmacodynamic properties: acute and chronic tolerance, absorption, distribution, and onset and duration of action. The specific biochemical distribution of glycosides was a prominent endeavor, and led to the conclusion that the heart absorbs eight times more glycoside than the organs of the belly and 30 times more than those of the eviscerated animal. The criterion was arrest of the heart within 40 minutes (1925–1935). In 1948 Geiling et al. and Fischer et al., using radioactive digitoxine, found no preference of absorption by the heart over the liver and kidney while containing much more glycoside. They do not deny the difficulty of extracting the C^{14} digitoxine out of the organs. However, all authors agree about the selective activity of glycosides on the heart. Thus an unpleasant discrepancy of concepts remains worthy to be tested again with our functional method using C^{14} glycoside. The variation in the binding of glycosides by serum protein was studied with E. Sutter, now professor in Gainesville, and Mrs. Kallenberger, and found to depend primarily on the number and position of the double bonds of the ring system. This phenomenon was responsible for the transport and the onset and duration of action. A simple experiment done in 1927 was instructive: an isolated frog heart at standstill from glycoside intoxication started to beat again more quickly when serum rather than Ringer solution was used for washing out.

Touring and lecturing in the United States in 1948, I met E. Cohn, expert in serum protein fractions, in Boston. He could not believe that the albumin fraction was the binding protein. I agreed to repeat the assays with all his pure protein fractions. A blind study was started with a 4 per cent control solution of fraction x; it provoked standstill of the isolated frog heart as well as of the heart of the cat heart-lung preparation. Dr. Kraye controlled the batch with the same result. It was the albumin fraction, purified by decanol which proved to be extremely toxic, since the retained decanol sufficed to kill the hearts. The final result was the confirmation of our concept that only the albumin fraction bound glycosides.

One day I asked my collaborator Konzett, now Professor in Innsbruck, if he would make use of his skill to find out if cardiac glycosides might affect the synapses of the perfused superior cervical ganglion with the nictitating membrane as an indicator. Astonished, he looked at me inquiringly for the reasons. The outcome was a surprisingly strong potentiation of the effect of acetylcholine, choline, and KCl at threshold doses of 0.5–1.0 for scillaren A. The effects were somewhat weaker with other glycosides. This finding of an interference between glycosides and the prominent transmitter in neuronal processes opened new problems not yet exhausted, but worth testing.

CLINICAL EVALUATION

I confess that in my practice as an industrial pharmacologist, the matter of the clinical evaluation of drugs was a captivating subject, although of the utmost delicacy. I have to limit my remarks to some major elements, merely to show how facets of this apparently simple problem have been changed by inconveniences not essentially related to it. The subject cannot be discussed

without mentioning that, historically, drugs were originally prepared by physicians, later by licenced pharmacists, and now by anybody who likes to do it. Actually only the expert chemist can compete. This trend is the logical result of the extraordinary development of chemotherapeutics and in the pharmacological and clinical evaluation of drugs.

No one with common sense can deny that clinical evaluation is an absolute prerequisite of any further progress in therapeutics. This is a matter exclusively of medical concern based on the consensus of two kinds of experts, the pharmacologist and the clinician. The pharmacologist submits only drugs the tolerance and effects of which have been studied according to the present state of our knowledge and the recommended dosage proven safe on volunteers. The clinician, an experienced physician, and not a youngster, proceeds according to a thoughtful plan on selected patients, who are informed that a new drug will be assayed.

Since the clinician is not a pharmacologist and clinical trials are also pharmacology, pharmacological advice is wanted during the performance too. This supposes some clinical experience in the pharmacologist. Also he should be an M.D. for the following reason. Clinical evaluation as a medical problem has its own responsibility and ethics, inherent in or acquired during medical education. Only this particular aspect of personal honesty, responsibility, and ethics, I believe, can relieve the actual unsatisfactory situation and prevent further undesirable interference. The latter comes from both sides. The way for improvement I see, on the one hand, is the creation by serious pharmaceutical houses of an association with membership based on acceptance of the foregoing ethical claims for clinical evaluation. On the other hand, the medical corps should form an analogous organization requiring adequate measures for correct performance of the assays, and objective precise interpretation of the obtained results. In this context, the pattern of the former Council of the American Medical Association may be recalled. An intimate collaboration of these voluntary associations is naturally supposed.

Such devices can minimize governmental interference for protection of the patients. As the situation stands, the interference could increase until it became a serious hindrance to therapeutic progress.

Another item related to this problem has to be kept in mind. Medical education does not provide enough critical knowledge about drug treatment compared with that for diagnostic training. But in practice both are of equal importance. Furthermore the practitioner gets his knowledge of old and new drugs primarily from pharmaceutical houses, whose claims are attractive but not always objective, while more disinterested information from the academic teachers of pharmacology and clinic would be preferable. In fact, there are enough, though often inconsistent, publications for making up a clear judgement by the too busy practitioner.

Finally, it must be remembered that every clinical evaluation of a new drug runs a risk because not all elements of safety are known. But seeing how unhesitatingly modern man in our technocratic era tolerates other much more dangerous risks, such as traffic casualties, one has to admit that the

risks of clinical evaluation are minor by comparison; this the more so, considering the scope and purpose of this procedure. I do not underestimate the difficulties of my suggestion of more noble behaviour than the present. The experiences of my career prevent that. But they shall not prevent my believing that, with goodwill and intelligence of a younger generation, things can be changed.

Among others three failures need mention. Investigating the morphine-free fraction of a Persian batch of opium, I observed an unusually high spasmolytic activity which was confirmed by clinical evaluation. At the very moment of introduction of the drug, all had to be stopped because this high activity could not be found in other batches of opium, and a thorough chemical and pharmacological analysis did not solve the mystery. More unlucky and warrantable was the event with the forerunner of thioridazine, a pyridinic phenothiazine derivative. Only some days before the presentation of the pharmacological and clinical qualities to the psychiatric association was it shown that high dosage and long treatment with this drug could induce retinitis pigmentosa. Manufacturing insulin requires reliable blood sugar tests in series. My attempt to change from a semimicro to Bang's micromethod failed when an expert from a clinical service was engaged. My doubts in his results occasioned blind tests for control of his honesty; what emerged was absolute nonsense and I got rid of him.

But I would conclude with a happier, event. In studies in tuberculosis with my associate, Undritz, the relationship of localization of the disease in the lung and other organs to usual position got an unexpected impetus. Visiting the London Zoo, I was attracted by a terrible quarrel produced by a dozen *Pteropus*. Observing their usual position, hanging head downwards, I thought this animal suitable for proving the localization theory, i.e., if in man with usual upright position localization was in the apex parts, it should be at the basal parts in *Pteropus*. The experimental assays confirmed this hypothesis.

But enough talk of my laboratory experiences and events. The subject brings us in contact with most chapters of pharmacology: hypnotics and sedatives, local anaesthetics, various kinds of alkaloids and glycosides, spasmolytics, insulin, peptides, bile acids, antihistaminics, phenothiazines, calcium, iron, antimony, and with cancer and tuberculosis. Problems of circulation and of the autonomic nervous system were my particular concern. In close and amiable collaboration with a respectable number of regular associates, transient co-workers from many countries, and graduates, a work of over 400 original papers, monographs and lectures issued, I owe to them all, as well as to the technical and clerical personnel, my heartiest thanks for the unfatigable and sincere, imaginative, and enthusiastic efforts, for their dignity and responsibility in their work as investigators or correlators between experiment and clinic.

The reader, expecting some comment with regard to the general and special atmosphere of working conditions as an industrial pharmacologist in a huge organization, will probably be disappointed. Having no sense for gossip

or ability for gossipy style, my comments will not be humorous. Any agglomeration of a certain size, organized in successive ranks, is compulsorily a place favoring driving human qualities: ambition, competition, prestige, and authority. Serving as balanced stimuli for collaborative efforts they are gratifying, but disturbing when personal. As a novice in "hierarchic machinery" and primarily preoccupied with development of my professional work and collaboration with the other sections of the department, I was slow in perceiving the general trend. Being for years the only physician, I had a pronounced ethical concept of the purpose and trend of a pharmaceutical firm. However, I confess frankly that in this respect I never had conflicts. I remember with thanks and pleasure the harmonizing collaboration and friendship with the advertising department's heads, Drs. Wagner and Court. While I was learning that chemists, business, and financial men tend to govern the field, my final admission as an executive officer was the acknowledgement of my department's contribution to the success of Sandoz pharmaceuticals without renouncing my medical policy. As far as I know, this is an infrequent event in pharmaceutical houses. How this has changed since I left eight years ago, I do not know. But I fear that marketing has become more important than candid advertising, in accord with the universal trend of our money-minded epoch.

Some impacts I felt disturbed the climate and course of work. There was the incongruity between the number of chemists and pharmacologists, the latter being in the minority. That was obvious but understandable when I started. However, I believe this state exists still in well-established firms. Yet current techniques facilitate greatly the speed of chemical performance, especially synthesis; this trend leads usually to a series of derivatives which have to be screened if valuable compounds are not to be missed. On the other hand, the demands for a thorough toxicological and pharmacodynamic analysis are also steadily increasing, and the techniques are more complicated and delicate. An equilibrated balance of personnel will not only avoid resentment of the respective chemists, but give more satisfaction to the pharmacologist and, last but not least, less loss of time for the firm.

With regard to the relative position of the chemist and the pharmacologist, the latter is handicapped, inasmuch as the discovery of the chemist is patentable, and this provides an official certificate of his effort reckoned in his advancement. The findings of the pharmacologist are not patentable, which is as it should be. But some chemists tend to consider patents as a necessary demonstration of their own efforts.

This is not to question the quality of the performance of chemist and pharmacologist; they are equal, as are the roles they play in the collaborating organization. What I mean is that finding an unexpected effect or a new indication for a drug demands as much knowledge, imagination, and luck as to find or synthesize a new substance. What good would a patented substance like Prontosil have been if Domagk had not discovered its bacteriostatic activity; and what would the situation for ergotamine have been without the new indications?

ACADEMIC ACTIVITY

Arriving in Basle I went through the ceremonies for the *privat-docent* again. I had no official function except the right to lecture. The audience depended on the few students attending lectures not included in the official schedule of examination. My topics were general physiology, vitamins, and endocrinology. Often my listeners were my nonmedical friends coming for interest or pity. Very exciting was a colloquium organized by lecturer friends of six different biological disciplines including psychology, providing the needed discussion of general and special topics from different angles. I was lucky in being charged in 1934 to lecture on pharmacology for pharmacists, illustrating the lectures with a voluntary well-attended experimental course. In the same year I was nominated for (extraordinary) professor and member of the faculty through the efforts of Edlbacher, professor of biochemistry. When our daughter of seven years was told that I was now a professor, she said "I would prefer a king." Concerned in all problems of the faculty and ready for active collaboration, I was often consulted when professorships had to be filled, because of my close contacts with scientists and clinicians in and out of the country. It was a great satisfaction to be elected one of the four delegates whom each faculty of medicine nominated as members of the Swiss Academy of Medical Sciences, founded in 1943. The members are re-elected every four years. Its activity is more a council for advancement of science than a classical academy of immortals. I was honorary treasurer for eight years. I still enjoy active collaboration in the daughter section of the Academy, the foundation for fellowships. Interestingly enough, the expenses of the Academy, as well as of the foundation, were primarily supported by the Swiss pharmaceutical plants until a year ago, when the government, through the Swiss National Fund for Science, contributed an equal amount to the foundation of fellowships. It seems opportune to mention that the government gives free hand to responsible scientists in the use of the money.

Two years after my start in Basle, I was tempted the first time to accept a chair in physiology or pharmacology. However, I found that to leave all the incompleted work was inopportune for me and unfair to my employer. Furthermore, I already had experienced the great difference in the ease of getting the necessary personnel. The second time, my postulated program for teaching, practical exercises, and active collaboration with the clinicians seemed too revolutionary to be acceptable, so I refused. The last challenge in 1943 went as follows. After I had given two solicited lectures to the medical corps and the staff of the medical school in Geneva, my wife and I were invited for dinner by Mrs. Frommel, the charming wife of the pharmacologist. To my surprise, besides some colleagues, the minister of education, the rector of the university, and the dean of the faculty were at the party. Only from their speeches did I learn the purpose of this pleasant adventure, to secure my agreement to succeed my teacher, the late Professor Battelli. Thanking them for their generous offer, I appealed urgently for the division of this position into separate chairs of physiology and biochemistry and for the engagement

of two younger experts I had in mind. The happy result was the appointment of these experts, O. Wyss and F. Leuthardt; and I remained in Basle.

TRAVELS AND CONGRESSES

The review on travels and congresses has to be limited to some general impressions. Details would need more semantic ability. I had the joyful chance to visit all the main countries of old Europe, North and South America, India, Pakistan, and Egypt. While comparing nature and people with my own country, my travel hobby was to see under which other conditions man is as happy as with us. I learned that it depends less on comfort than on inner poise as long as conditions are not injurious to health and morals. An illustration: When I asked a relaxing porter in Naples to carry my luggage, he smilingly answered: "Grazie o già mangiato [Thanks; I had my lunch already]."

These trips must have been numerous since I was called a globetrotter. The contact with colleagues in their institutes and clinics, the lecturing and exchanging of ideas on professional and personal topics, were of great benefit, enlarging my knowledge and resulting often in long-lasting friendship.

With regard to Congresses, opinions are contradictory. That is merely a personal affair. I share the view of the late Magnus that an observer learns more in a day in a well-programmed meeting and by mutual conversation than in a month of reading. To see, hear, and contact the prominent personalities is, or should be, an event for the beginner, and to approach them is much easier in a friendly social atmosphere. It usually enhances, though sometimes diminishes, the impression one gets by reading their work. The stimulating effect of some international forums is obvious, but adverse results may happen. I found Szent-Györgyi in a unusually sorrowful mood, after his lively report in Rome in 1932 on the presence and function of Vitamin C in adrenals. On being asked the reason, he said, "Did you not see that nobody believed what I reported?"

"Do you really believe it yourself?" was my question.

Shocked he gave back, "Of course I do."

"Well, dear friend, that must suffice you," was my reply; and he laughed and was gay again.

But instead of talking on these subjects, I would like to refer any sceptic to: "A Short History of the International Congresses of Physiologists" by K. J. Franklin in *Annals of Science* (A quarterly review of the history of science since the renaissance, 3, 242-335, 1938) for a most instructive discussion of the pros and cons. The reader will learn that such events of the international community not only pursue scientific purposes but have eminently important social and even political aspects.

The segregation problem between physiology and pharmacology, now settled, has its own history. Personally I regret it, and so I believe do most of my colleagues in the former Council of pharmacology. The main reason was not of scientific nature, but merely the fact that pharmacologists have long had the feeling that they were not taken as equals by the physiologists despite the enormous progress pharmacology had made. Fortunately, one link remains in the common meetings held every three years.

As a personal adventure I refer to the 16th Congress in Zürich in 1938, with Hess as president and myself as secretary general. The congress was the jubilee one, the first having been held in Basle in 1889. Among the duties of the Swiss committee were the registration according to respective national organizations and the printing and circulation of the presented reports to members some time before the congress. Both these duties were mine. The latter was managed by the good will of the reporters and the efficient collaboration of my associates, Drs. Gehlen and Schalch, and the secretary, Miss Sievert. The control of membership was very much handicapped by the uneasy world conditions, particularly by the threatening posture of Nazi Germany. Without going into the details of the troubles we were put to for displaced colleagues of high esteem, I relate the following adventure. In the spring of 1938 coincident letters from Cannon and Dale advised the Swiss committee that if O. Loewi were still in jail—called “schutzhaft”—during the Congress, contacts between American and British on the one hand and Germans on the other, would be impossible. With these two letters I went with my wife to meet two competent adepts of the conscienceless Nazi system, one in Heidelberg, the other in Munich; the daughter of one was Hitler's godchild. Unexpectedly, within a fortnight Loewi wrote me that he was free and allowed to emigrate, but not without paying his tribute—from the Nobel prize—to the inhuman, money-greedy system. This outcome was favourable for the Congress though not for the Loewi family. The “coded” correspondence I had as mediator with Mrs. and Mr. Loewi reads like a passion, starting in February 1938 and ending in February 1941, when Mrs. Loewi wrote me that she would sail from Portugal to Argentine where her son was a co-worker of Sandoz. Finally, she would be able to join her husband in New York. In him, personal vitality and hopes for a reunion with his charming and courageous wife alternated with breakdowns from time to time. The critical phase was September 1939 when Loewi wrote in a footnote in his letter, “Don't believe that I shall commit suicide.”

That is but one of the countless disastrous fates. Not all had an outcome as favourable as that of Loewi. His indestructible vitality and belief in science let him forget the past and look to the future.

GENERAL CONCERNS

A 50-year career invites an account on some general concerns of pharmacology. The International Congress in Zürich seemed to me the challenge for discussion of the topic “The scope and future in teaching and research in pharmacology.” H. H. Dale and W. Straub as the reporters agreed in essence with the claims of the founders of pharmacology, Buchheim and Schmiedeberg, in stating that “Pharmacology has not to deal with or to teach practical therapeutics but to provide the scientific basis of knowledge concerning the action of remedies on which a rational therapeutics can be built” (Dale). As a well-trained physiologist, Dale promoted the scientific basis of the problem, i.e., how a drug acts, while Straub represented the classical pharmacologist tending more to where a drug works. In short, Theory versus Practice.

But what about teaching? In this respect I saw, and still see, a gap in clini-

cal evaluation. Therapeutics in clinical and medical practice, being pharmacology in man, needs pharmacological thinking and performance as well as clinical experience. This efficient combination in teaching students and practitioners is far from being realized. Both get their therapeutic information mainly from pharmaceutical houses, often with collaboration of the academic corps, and admittedly in an often instructive and attractive form.

The change of pharmacological research in the last 30 years is remarkable, due to the tremendous advance in our knowledge of its scientific basis. New physical and chemical methods have fostered our morphologic, functional, and particularly biochemical thinking. The study of the effects, the "Where" of the action of drugs, as well as the "How," came to have new meaning. But no matter how promising all this new knowledge may sound for the younger generation, I cannot but remind it that general biological problems remain unsolved, such as the transformation of physical and chemical energy in any physiological performance.

Education, scientific information, and documentation are general concerns I may refer to briefly. Reforms in medical education are discussed and tried everywhere. Teachers usually are too concerned with tradition and not enough with obsolescence; i.e., they are reluctant to adapt to the current state of knowledge, forgetting that science is a dynamic evolutionary affair. While historical information of the development of a problem is wanted, the era of encyclopedic knowledge has gone. The difficulty remains in stressing the essentials by omitting unnecessary details.

The two concerns, scientific information and documentation, are as urgent problems as organization of education and research. It is a fact that today no scholar can satisfy conveniently his desire for knowledge even in his own speciality. Unsound competitive promotion of science, supported by grant systems (governmental and others), not only increases production unduly but devaluates the quality of papers as well. Of course I speak only about the questionable ones, but unfortunately they are in the majority. According to the slogan, "publish or perish," the number of papers, i.e., kilography, seems often more decisive for the future of a young scientist than their creative content.

As a pharmacologist and editor I censure the frequent neglect of one of the basic rules of pharmacology, the significance of individual dosage. Since drugs are used now in all kinds of medical research, this ever present rule for animal and man has to be considered if results should be consistent. I am reminded of the pertinent data by Hanzlik (1913) for salicylic acid and Augsberger (1953) for cardiac glycosides showing a ratio of 1-10 to produce the same effect in man as in animals. How limited is the value of using one dose only for all individuals. The most efficient remedy against these deficiencies must come from the scientists themselves inasmuch as "brains" have to subdue "hands," remembering the motto, "Non multa, sed multum."

With regard to documentation we touch rather a hotter iron. Documentation is not an egoistic purpose. It serves science primarily, and science is a noble property of an international community. There is nothing to justify

the present inconvenient state of its literature. The causes have various aspects: scientific, technical, national, and commercial. How to harmonize them? The foregoing chapter related some scientific obstacles. Several attempts made by publishing houses, stimulated by scientists, to concentrate and simplify the present documentation systems have failed, either because of national or commercial factors. However, I believe there should be no economic difficulties, because I venture to say that an adequate organization achieved by national and international cooperation would be less expensive than the present multi-system. Although the wonderful efforts by publishing houses and libraries are highly appreciated, it is, nevertheless, practically impossible to get a complete documentation on a given subject. There is not only a need but also a possibility of greater efficiency by concentration of all efforts, cooperation, and collaboration, accompanied by goodwill and disinterestedness of scientists, editors, publishers, and librarians on the national and international level.

Retirement came unexpectedly and as an unpleasant adventure because of its short advance notice and my unpreparedness. Despite the warnings of my wife, I was relying on wrong premises. I had hoped to have the chance to work in a small laboratory on some problems I had in mind. But the atmosphere was inhospitable, and I was only sent to and fro between negotiators. I declined spontaneous offers from many sides, university and industry, preferring complete independence. But needing an adequate occupation I found a satisfactory solution in contributing to international organization of the new research field, neuro-psychopharmacology. The C.I.N.P., Collegium Internationale Neuro-Psychopharmacologicum, was founded in 1957. As its president, I prepared the first meeting in 1958, in Rome with Trabucchi, then the second meeting, 1960, in Basle with Labhardt. At this meeting I became, as P. Hoch, my successor said, "grandfather" of this organization. At about the same time (1958) the international journal *Psychopharmacologia* was started in the most pleasant collaboration with A. Wikler, published by the Springer-Verlag. Four and a half volumes have appeared, but if we could have accepted all presented papers, the number would have been 40 per cent higher, with much less trouble and work. Now I desire to become "grandfather" of *Psychopharmacologia*, too, for, having passed 75 years, I would like the rest of my remaining time for myself, while alert to news of science.

The picture of my career would show an undeniable gap if I did not mention the share my family had in it. If I have learned by errors in my professional affairs, I was unmistakably lucky on the family side. My matrimonial companion is interested in any kind of culture, and is responsible for my not being drowned in professional and social obligations. Having all reliance in her, I could discuss delicate and confidential events without fearing indiscretion. I confess rather that these discourses clarified my concepts; and not infrequently when I disregarded her intuition and followed my rational reasoning, I took the wrong way. Both sides learned that decisions for oneself fail mostly for emotional reasons, and that frankly conversing favours understanding and harmony.

My health was and is fairly satisfactory, even though I have always been prone to bronchitis and have had rheumatic disease and duodenal ulcer. Fortunately I endured all and have never had to be hospitalized. Geriatric symptoms are now appearing in slower adaptation to changes of climate—Basle is known for heavy air. What disturbs me more is the increasing loss of fresh memory and intolerance to tobacco and alcohol, which followed an accident in 1962. The broken humerus healed within two months, but cerebral impacts vanish slowly. I miss the previously favorable result of consultation with my unconscious in the solving of professional and personal problems while sleeping.

Concerning hobbies, as a favorite pursuit followed persistently, I have to offer my concern with research and research application. It is said that the idea of work is an ambiguous heritage of Western civilisation. I hope indeed that in my case suitable antidotes cleared the ambiguity. Leisure, as freedom of any occupation, I do not know, inasmuch as the entertainments I enjoy do not fit the definition. Of the multiple pleasures offered by nature, I benefited according to age, society, and season from climbing, walking and riding, sledging, skating, skiing, and curling. For 27 years, mostly up here at the Rigi where we have our tusculum, and where these lines are written in view of the Alps, we have vacationed. Other diverting exercises were dancing, bowling, shooting, tennis, and playing cards. As I have mentioned I was for a time a fervent violinist and singer. All that at its time and with measure. Daily physical exercise is still a need even if only a dozen knee-bends. The possibilities of car driving have been explored since 1912 and now the yearly drive on the "Autostrada del Sole" is still a dream. When the marriage income allowed us to acquire paintings instead of copies, step by step we started to adorn our home with some examples of various periods. Our understanding does not extend beyond the epoch of Rouault, but we have a nice collection of the new trend in the gifts of our young grandchildren. While a student, I belonged to a corporation where I found faithful friends, but becoming a veteran, I have avoided any social or political clans. I have had the chance to enjoy a circle of friends having very disparate occupations but being in essence of the same mind. To become carrier of the "Paracelsus-Ring" bestowed by the town of Villach, Paracelsus' second home, made the deepest impression on me. I retain a high esteem for this volcanic but imaginative and stimulating countryman.

In growing older it is advisable to set up a physical and mental order to prevent the atrophy of inactivity. Nature invites the first, and exciting scientific news, the second. But leaves get yellowish, soon brown and dry, and a weak blow will make them fall.

Nevertheless, taken all in all, it was a wonderful experience. If I have any advice to give to my friends and colleagues and especially to the younger of them, it would be Rousseau's words: "L'homme qui a le plus vécu n'est pas celui qui compte le plus d'années, mais celui qui a le plus senti la vie."