SCIENCE AND FATE

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When the life story of a German pharmacologist is related in conjunction with his scientific work, it also involves a narration of the difficulties which beset German Science during the decades following the First World War. The political events were often so overwhelming that one could hardly escape them.

Before the First War, everything ran smoothly. I myself, born in 1898, lived in a wealthy businessman's house in Gilgenburg, a small town in East Prussia, amid lovely surroundings and lying between lakes. In spite of its remote situation, I came in contact with scientific personalities early in life, because two close relatives (the physico- and photo-chemical Professor Luther, and the food scientist, Professor M. P. Neumann, known as Bread-Neumann) spent their holidays with us. It was thanks to them that I, at nine years of age, was able to go to the nearest "Humanistische Gymnasium" (High School) of the district town Osterode. The quiet pursuance of my education was completely disrupted by the beginning of the 1914 War. As my small home town lay only a few kilometers from the Russian border, we learned the horror of war from first-hand experience. Crossing the battlefield, where many dead lay, left a terrible impression on me, without my realizing when only 16 years old, that I myself would have to take part in these events as an active soldier two years later. In 1917, in one of the greatest battles in France, I came in contact with chemical warfare, something not without influence in my choosing the profession of Pharmacology and Toxicology, and an interest in this subject continued. After the end of the war, I began medical studies in Königsberg and Munich, with well-known and respected teachers. After the "Physikum" (pre-medical examinations), I wanted to change over to Chemistry. I took several semesters in the major chemistry practicals with success. But times were uncertain. As a doctor, one can always hope to be employed in the most desperate situations; not so as a chemist. The situation was difficult for us. There were days when we had practically nothing to eat. My father had completely lost his fortune as a result of the inflation.

I did my "Doktor-Dissertation" on perchlorate, under the supervision of Professor Hermann Wieland in Königsberg. This was a subject to which I always returned. In the so-called "Hofmeister's Reihe" (lyotropic series), I

classificd the position of perchlorate beyond the thiocyanates, which until then had occupied the last position.

In the Institute at the same time were Berend Behrens and Paul Pulewka, with whom firm friendships were formed. During difficult times, that happened more easily, as we found out yet again in the years after 1933. During almost the whole of the year 1924, I had to work as a medical practitioner due to lack of money. House doctors could occasionally have lunch in the hospital and even for that they were grateful. In contrast, I did well in general practice. Nevertheless, at the end of 1924, I accepted Wieland's invitation to return to his Institute, without pay. That time spent in the Institute was very stimulating. In 1923, Behrens began to work with isotopes of lead, but no money was available and he had to abandon these experiments. And so Hevesy remained alone in this field for the time being. Frogs and mice were practically the only experimental animals we could afford and we had to build our own apparatus.

From April 1925 until the end of the year, I worked in the Medical Clinic of Professor Krehl, in Heidelberg. This stimulating time was the nicest of my years as an Assistant, not only because of the brilliant personality of Krehl himself, but also because he would discuss anything, even his own mistakes. He was great enough to admit his own mistakes or to seek the advice of young assistants in the field of pharmacology. A few future Chair-holders, Professors Reinwein, Bohnenkamp, Dennig, and Hoppe-Seyler, who lived in the Assistant-wing of the hospital, guaranteed high levels of discussion. At that time, Bohnenkamp had completed his work on heat production by the frog heart. Hill's measurements were awarded the Nobel Prize, showing how highly these results were esteemed. Unfortunately, I later discovered that the method was not foolproof.

External conditions influenced my themes of work again and again. My work deviated from a chemical theme when I went to Düsseldorf in 1926, to Professor Hildebrandt's Pharmacological Institute. There, the money available was greater than I was ever to have again, though it was unfortunately administered through dreadful bureaucracy. This favorable financial situation enabled me to carry out many costly experiments, using cats and dogs, only for the sake of methodology (e.g. operations on the central nervous system, Starling's preparations etc.). Much work was done on Cardiazol (Metrazol), as well as on acetylene, which had been introduced by my first teacher, Wieland, as an anesthetic but had not yet been investigated with respect to its actions on the circulation. In spite of its minimal effects on the circulation, acetylene could not be used as an anesthetic because of explosions. We tried, in vain, to find something that would make it nonexplosive. At this time, I came in contact with the American Anaesthetists' Association.

During our diverse and many-sided experiments, the different characteristics of research became clear to me. One can explore a subject systematically, an approach favored today, if only on economic grounds. Research

workers who use this approach cannot be overlooked. Here, I am thinking of Feldberg or Koelle in acetylcholine research (of course, also Loewi and Dale), of Euler and Holtz in work on adrenaline, Lendle and Repke on digitalis, etc. One can work this way in a small field, for even in the smallest, one is still guided by all the laws of nature.

The other approach is that of the adventurer (*Adventures in Biochemistry,* a book published in 1931 in honour of Hopkins). In this way one may discover a great deal right away; important discoveries are frequently made but luck also plays a part. A particularly successful research worker using this approach is Selye. But danger lies therein: quisquis ubique habitat nusquam habitat (Martial).

Perhaps I myself had a tendency to work this way but benefited less by luck. However, in the initial stages of my work, purely theoretical ideas played a role. At this time, I reasoned out the spatial propagation of chemical reactions in a homogenous system [something like a model of nerve conduction (Meinecke 1)]. In a heterogeneous isothermic system, for example, in the super-cooling of molten substances, it is a frequent occurrence. Reactions that are spatially propagated are autocatalytic. In this way, the oxidation of oxalic acid by permanganate takes place. More easily understood is the oxidation of arsenious acid via bromate. If some potassium bromide is present in the solution, then the reaction proceeds as follows: $BrO_3^- + Br^- \rightarrow BrO^- + BrO_2^-$, which then converts the arsenious acid to arsenic acid. When a small amount of potassium bromide is added to the solution in a test tube the reaction begins immediately and propagates right through the tube, at first slowly and later at uniform speed, as long as substrate is available. The limiting factor is the diffusion of the newly-formed catalysts; thus a slower reaction at the beginning. One can formulate an approximate equation for the process: $v = a\sqrt{C.K.D.}$ For nerve conduction, this model equation gives much too slow a propagation speed. C cannot be increased and K is the reaction constant. The limiting factor is D, the diffusion coefficient. If one applies this to a heterogeneous system, as in a living organism, the diffusion on surfaces may be enhanced, as in the experiments of Scholander (2) and Ens (3) who showed that the diffusion of oxygen in the presence of hemoglobin, for instance, in membranes, could be increased eightfold, a result which could not be achieved by the partial differential equation alone. Also, if one observes the speed at which oleic acid propagates on the surface of pure mercury, what possibilities may exist? One would expect that the reaction speed could still be increased. That would be so, but for a further postulate—namely, that the reaction takes place continuously but the catalyst is constantly being removed as soon as it is formed. Only if an initial stimulus provides a greater amount of catalyst, which exceeds the capacity of the metabolic processes, can a reaction wave proceed over the nerves. At that time, Gerard, with Hill and Hartree, measured heat production in nerves and found continuous heat production, which was increased only slightly by stimulation. This semed to agree with these ideas.

Nevertheless, these reflections were abandoned and another example was sought for an autocatalytic reaction. I believed then that blood coagulation could be such a process. However, attempts to construct suitable apparatus to pursue this idea had to be abandoned because the time in Düsseldorf had come to an end. Everything remained at the theoretical level. "It lies not to me the truth to proclaim, but the truth to seek, and to reveal it for discussion" (according to Goethe).

Experiments were then begun in two different fields. We demonstrated tachyphylaxis of histamine, but further pursuit of work with histamine was forcibly interrupted again and again. Another line of thought led to the idea of teleology, which is a horror to the natural scientist after the philosophy of nature of Schelling and Hegel. But for me, the important statements by Kant in "der Kritik der Urteilskraft" were constantly relevant. Kant said that objective thoughts can represent only a regulative principle. Thus, to determine the real, ultimate objectives, one must have an overall understanding of the aims. Goethe called this one of the fundamental faults of the Greeks, e.g. Aristotelians, that they immediately jumped from an observed phenomenon to an explanation as psychoanalysts often do today. We judge only by the nearest observation, consequently we judge imperfectly and in only a temporary and therefore regulative way.

We tried to eradicate teleology from these thoughts using the Principle of le Chatelier. It is derived from an inanimate system and its statement denies any trace of teleology. Also, the conception of regulation should not appear, although elements of entirety are inevitable. Considering the analysis by Jendrassik (4), perhaps the idea of opposition is more readily applicable although it deals only with a descriptive connection. For example, in hypocalcemic tetany, calcium released from the muscles relieves the tetany. Indeed, some contracture of the muscles is connected with it, but this is a rapid reaction. Due to the tetany, lactic acid is formed which increases ionisation of blood calcium with consequent delayed calcium release from the bones which has a lasting effect. Such antagonisms are found in poisoning by sodium chloride and sodium iodide, both of which exhibit only the regulative principle (O. & L. Eichler, 11).

Still another trivial but well-known example: after an infusion of glucose, there follows a secondary release of insulin, which lowers blood sugar to levels below the starting point. Such effects are to be found with every action of a drug, being not fully congruous with the concentration of the drug, so that one should expect evidence of an opposing effect, as with the dose of glucose.

Following this principle, an action of adrenaline on release of histamine was sought and found. After a dose of adrenaline, a secondary hyperemia was observed not as a result of release of histamine from mast cells but according to Schayer, and often confirmed, by activation of histidine decarboxylase.

These thoughts were pursued further in Giessen where I went in Octo-

ber 1928 with my chief, Hildebrandt. There working conditions were very much more difficult and disclosed all the economic difficulties of the time. The budget was minimal. Without support from industry or from the "Notgemeinschaft der Deutschen Wissenschaft" (from which only limited funds were available) work would not have been possible. I was the only Assistant, and if research students applied, no technical assistance was available. It was quite impossible to pursue the expensive experimental projects of Düsseldorf. Also, that was not expedient considering the construction of the Institute. There was one large room directly above the lecture theatre, with a poorly supported floor. Every step caused swaying so that sensitive recording could not be used. Then there was a small room which served as a library (Naunyn-Schmiedeberg's Archiv and Ronas-Berichte were the only Journals), and balance room, and also housed a Leitz colorimeter. Another small room was suitable for chemical experiments. Therefore, there was a spontaneous turn towards chemical problems, with the exception of primitive toxicology studies using a combination of narcotics and analeptics.

Now the mathematics which had been formerly nurtured came to the fore. When I was with Krehl, I had already instructed some Assistants in differential and integral calculus. Now I studied the theory of functions, topology, elliptical integrals, partial differential equations, and calculations on variations and integral equations. One might rightly ask why I sacrificed so much time. I was attracted by some results of Hartridge and Roughton on the shape of erythrocytes, which is an interesting and relevant problem. In a rotating body, the oxygen molecule must attain the greatest possible saturation in the shortest possible time. Naturally this would be accomplished with the given amount of hemoglobin being in a flat body which, however, requires a greater surface area. This must also represent a minimum for economical reasons and therefore becomes a secondary condition; the problem of Dido. It seemed to me that a relationship between the structure and the dimensions of the pulmonary capillaries must emerge for each individual animal species. Many calculations concerning this were later lost and could not therefore be published.

This made me ask whether such an extensive pursuit of these problems is necessary for an individual research worker. To collaborate with a mathematician is always necessary but, in my experience, fruitful collaboration is difficult unless the researcher has some knowledge of mathematics. A mathematical exercise also serves as a training in the formulation of ideas, quite apart from the esthetic pleasure of the thoughts. I personally could not derive corresponding profit from the time spent on it, because after 1933, life simply did not allow uninterrupted work. But sometimes, one cannot otherwise encounter challenges. For example, with analytical functions of the theory of functions, if one knows the value of a function for the border of a surface or a space, one can then calculate any value for the inside. Could that also be possible one day for the structure of a cell? Anyway, this idea led me to investigate some of the chemical properties of the cell surface and

to collect data, for example, from the surface of heart muscle cells where copper, magnesium, manganese, alkaline phosphatase, etc are bound. Using complexing agents, it was possible to release copper etc from the surface, or to inhibit the action of enzymes that require metals as coenzymes. By investigating some organic fluorine compounds, we found substances that formed complexes with manganese and magnesium and that inhibit alkaline phosphatase.

In Giessen during the summer semester of 1930 I qualified myself for teaching. The work was concerned with the anions in the lyotropic series. In this series, I added perchlorate, next to thiocyanate, as the final inorganic anion. In frogs, the symptoms of intoxication due to these two ions are practically indistinguishable. In general, there are close similarities as, for example, demonstrated by ion displacement in the thyroid gland. This also occurs in other organs that actively transport iodide, for example the bronchi.

I was specially interested in the mathematical formulation of the mechanism of poisoning, i.e. action depending upon concentration. As in the exact sciences, according to E. Mach, it is usual and easiest to express an effect proportional to an agent (diffusion, heat conduction). According to chemical kinetics, this assumption is often applicable to living objects as in the extensive application of the Michaelis-Menton equation in biology, especially as formulated by Lineweaver and Burk. These calculations are valid but only when one function is observed and for short observation times; whenever a longer period is chosen, the action is not proportional to the concentration in the whole animal. Also, after quantitatively-excreted substances, a slight action still remains. Today, it is usual to describe excretion according to half-life. Finally, one can express any curve as the sum of exponential functions. To explain it, the individual components are chosen arbitrarily. But if one reckons half the original concentration as half-life, then one is wrong because the next half-life expires in quite a different way. With the excretion of perchlorate in humans, I found practically only one component.

In accordance with physical nomenclature, e.g. with elastic bodies or magnetism, I proposed the expression hysteresis. Heubner proposed two expressions: pathobiose and allobiose. These would certainly be satisfactory for something like allergy or chronic poisoning, but for acute poisoning, hysteresis seems better to me. Thiocyanate and iodide were demonstrated as typical poisons with hysteresis (Eichler (5)). The expression presumes a proportional relationship between action and concentration. During the phase of excretion, a discrepancy occurs which is hysteresis. Here, there exists a link to the Ct-poisons which were introduced in chemical warfare and which are now used as carcinogens. Probably all poisons that cause mutations belong to this group (see Druckrey and Schmähl). However, this concept was rejected at a Colloquium in Geneva, 1969.

Also rejected, by Clark, was an idea that Straub had introduced follow-

ing experiments with muscarine on hearts of "aplysia." The poisoning would then be visible only when the substance was entering or leaving the appropriate organ. Here also we can assume that action is proportional to the concentration, magnitude depending upon site and time. In local regulation, it would be helpful to know concentration changes with time at various sites in the tissue. If a regulation occurs quickly, then an effect will be visible only during absorption. If the drug in question acts after absorption and binding to tissue it cannot have an immediate effect. For example, we have demonstrated (with Sebening) the absorption of atebrine in thyroid tissue. Fluoride behaves similarly, being taken up in the apatite crystal of the bones. The question is whether Straub's idea is congruous with these findings. One can develop ideas in accordance with which an action will occur, if two stereoscopically adjacent elements of cells contain different concentrations of a drug. Here I would like to quote from Goethe: "Theory for its own sake is without use insofar as it makes us believe that connections between natural phenomena exist." This quotation applies also to the following.

In my studies at that time, I arrived at various conclusions derived from statistics. If one tests the sensitivity of a large number of isolated organs, then one can always record a spread of the effect. If these single effects on the organs were not interdependent, the spread must ultimately increase tremendously because the individual squares of the variations are added together. Since this contradicts experience there must be connections that counteract. One cannot be content with a statement and call it a general regulation or axiom. This brushes aside the problem in which regulations on basic structures play a role, as in cases of poisoning. So, analysis of a collective deals with the question of why some animals are more sensitive than others. Concerning this, in 1930, I began testing the toxicity of thiocyanate and iodide on frogs and found that poisoning with a two-molar solution was significantly greater than with half the concentration. The osmotic pressures alone are much less effective than those produced by the corresponding concentrations of sodium chloride solution. We concluded that the primary site of action in the muscle should be sought (naturally, the central nervous system might also be affected but these anions are taken up to a lesser extent there). In detoxication, excretion of iodide takes place via the kidneys and the water available is an important factor. With a lower concentration of solution, some decrease in toxicity might be expected but not to this extent. The findings could be explained if the following correlation holds: frogs that are sensitive, are poor excretors. Those that are insensitive require less fluid for excretion. Later, another finding indicated that muscle was responsible in part for the improved excretion. The muscle fibers increase in volume and the extracellular space decreases. The concentration in blood remains the same but the surface of the muscle fibers increases, resulting in a less dense occupation of the surface. And so animals reacting in such a way are poisoned less easily. This decrease in extracellu-

lar space will also encourage excretion.[1] Nevertheless, all possible factors must be considered. Better functioning of the kidneys is necessary. In a later publication, the above statement was confirmed by various means. But direct proof was lacking because we could not determine the excretion ability of uninjured frogs. Obviously, the problems investigated were extremely theoretical and for that reason I began to search for compensatory work with direct practical applications as was called for in science after 1933. To satisfy this need, I lectured on air raid protection and did some organizing work from autumn 1933 to summer 1934. For that I was aptly suited because of my previous lectures on chemical warfare. Further time was spent on planning the reconstruction of a hut as a Pharmacological Institute. I did most of the planning but gained no advantage from it.

In October 1934 I was called to Breslau and took over the Institute that had been formerly administered by Professor Riesser. I managed to keep Riesser almost two years in the Institute. I placed one floor at his disposal until he was appointed to a research post in Switzerland. His work was very different from mine so that the Institute had practically no apparatus of use to me. The research allowance was 8,000 DM per month, for the entire staff. What was saved on teachers and research was spent by the Government otherwise. If I had not obtained help by Straub, from Hoffmann-La Roche for the acquisition of apparatus, work would have been absolutely impossible. Also, I obtained further aid from "Kaffee-Handel" and consequently I worked on coffee problems. So I had to work for industry, since they provided the money, and I was, in a certain sense, bound. We could not use the so-called "Schwarze Kassen" which had formerly been for financing research and paying technical assistants. According to the original ordinance of the Kultusministerium, industrial donations to Institutes had to be given to the University administration, which could undertake their distribution arbitrarily. When that happened resources dried up because the donors wished to be certain that useful results would be obtained from those supported. This ordinance therefore had to be rescinded.

Our statistical problems mentioned previously were pursued further from another point of view (Eichler & Smiatek 6). I concluded that with similar substances with approximately the same site and mode of action, the position of each animal in the curve of the collectives must be the same. To test this hypothesis we used three anesthetics, chloroform, Avertin (tribomoethylalcohol), and Eunarkon (a short-acting barbiturate). The doses were so chosen that from a group of 400 rats, around 50% were anesthetized. Further, a correlation of the two alternatives was calculated between

[1] From these experiments, based on general experience, I concluded that (with very few exceptions) inorganic anions are to be found only extracellularly. This opinion was later disproved by Conway. I had the proofs at hand that anions were able to enter muscle cells reversibly, but I was concentrating on another problem and did not pursue this important fact.

the substances. Between chloroform and Avertin the correlation was unequivocally positive. Both substances apparently act on the same structure as one would expect according to the theory of narcosis. Quite contrary to this, there was no correlation between Avertin and chloroform on one hand, and Eunarkon on the other. We concluded that they acted on different structures, which would comply with the conception of Pick on Eunarkon as a brain-stem anesthetic.

We then took up another question: whether the animals that were anesthetized (lying on the side) with the smallest dose were also the first to die. At death, the respiratory center is depressed, therefore one can expect a smaller correlation or none at all. With chloroform, the correlation coefficient amounted to only +0.40. With Avertin, no connection existed at all; a large number of the animals that were anesthetized with the chosen ED50 dose, did not die with the chosen higher dose, and vice versa. We see that the so-called therapeutic index itself shows a collective, i.e., there are animals with a higher and others with a lower tolerance to anesthetics. Also, between Avertin and chloroform there was no correlation, which indicated, according to our way of thinking, that they act on different structures, to cause anesthesia and to depress the respiration center. This interpretation reveals the single mindedness of our thinking in which, using statistics, we could find no more than a comparison on significance. Today, one would say that various different receptors in the brain were attacked.

Sometimes it happens that earlier "sins" recur yet again. Thus, while still in Giessen, I once read in a newspaper about harmful effects of caffeine on the reproduction of rabbits, with misleading publicity about it. I saw at once that almost fatal doses were being used. It seemed clear to me that a correction was essential. Our investigation was made with a dose (0.1g/kg) (8) which was still high, but endurable over a longer time in rats and was repeated without interruption over four generations without an adverse effect. This type of problem has assumed great importance during the last decade. In 1936, I again began experiments on coffee. Because of these experiments, I was invited to give the main report at the meeting of the Pharmacological Society in Berlin, 1938, on this theme. All this led to my book "Kaffee und Koffein" (9) and now the second edition is being prepared. With the financial support of Darboven (Hamburg), my co-worker Professor Vollmer began to investigate the action of diuresis on metabolism of minerals as a regulation opposing the increased excretion of sodium, etc. There was at that time no method for estimation of adrenocortical hormones. To obviate this difficulty, I again began to work on my earlier ideas regarding regulation. I concluded that if the caffeine dosage is suddenly stopped after a long pretreatment with caffeine, an induced counter-regulation should continue and become perceptible. Also, the plan was to introduce in Germany a method which was used in the U.S. with much success using a certain balanced mixture of inorganic salts from which many important re-

sults are still expected. With the much more effective diuretics available nowadays, this would be more effectively demonstrated.

In a concurrent set of experiments, we began to work on the metabolism of fats as influenced by caffeine. Everything was extraordinarily difficult because the Assistants were compelled to do military service. That could be done only during the term holidays, so that the most important time for work was lost. Ultimately, the two years' work by Dr. Hindemith, which had been giving promising results, was lost in the last phase of the war as we had to leave Breslau.

At the beginning of the war, I was called up and commissioned in the 6th Army for about six weeks in Poland, but from the end of November, was again able to continue my lecturing. To begin with, no importance was placed on scientific research. All the Assistants in the Institute were called up so that I had to give all the lectures. Furthermore, the enlightened Kultusministerium insisted that the students, granted leave of absence from the army to study, must be able to attend the lectures in any semester. This meant that lectures had to be repeated many times. Thus, I lectured 25 hours a week during both semesters; not practicals but lectures (Pharmacology I and II, 8 hours, for dental students I and II, 8 hours, medicinal plants, 4 hours, prescription writing, 2 hours. Pharmacology for pharmacists, 2 hours, industrial toxicology, 1 hour). Later I was granted an Assistant but then we had to take over work on war toxicology—the toxicology of explosives, mist, chemical warfare, and phosphorus combustion against which we had found an effective substance. The interesting research work was partly lost but in any case was not published. Nevertheless, the advancement of our other problems went ahead, even if slowly.

In 1934, Professor Wolfgang Heubner approached me about writing a book on the pharmacology of the inorganic anions (Hofmeister'sche Reihe). Earlier I had written a short article on chromium for the Handbook, which had pleased him greatly. By then I had worked for a long time on the Hofmeister'sche Reihe, so I agreed, particularly as I respected Heubner a great deal, and in the course of time I got to know him better. Finally, I wanted to see for myself what exactly had been done in this field. The literature was widely scattered and there was no generally accepted point of view. I worked intensively on it from 1934 to 1942, a hard time, since I did my work thoroughly (over 6000 references). There are certain laws that extend throughout the entire animal kingdom. The book dealt with different chemical properties—the precipitation of calcium by fluoride and phosphate, complex formation by thiocyanate, by pyrophosphate and distinct colloidal, chemical Hofmeister'sche effects, in order to gain an insight into pharmacology and into the inexhaustible theme of chemical and physico-chemical constitution and pharmacological action. Certain rules are to be found for colloids, enzymes, and inanimate membranes. But as soon as the whole cell is investigated with respect to the ions, all relationships cease, as though indicating how little we know about conditions within the cells. The Hofmeis-

ter'sche effect was found in whole animals in the same way as precipitation of calcium, but only with very large toxic doses. The action of thiocyanate and perchlorate on the thyroid had not been discovered at that time. Also, radioiodine was not yet in use as a more convenient and more sensitive test. But these two ions, whose actions appeared so easy to understand on this basis, showed differences on further inspection in spite of great similarity.

When one works for so many years on such a book, one learns a great deal. But more important are the consequences on further scientific research work. Many questions arose which I had not intended to pursue.

Investigations were begun on the frog heart with ferrocyanide and pyrophosphate, two anions of the Hofmeister'sche Reihe, which act identically on heart function. Here two different receptors in reaction constants, dissociation, exothermic heat, and chemical order were measured and calculated. It soon became apparent that the two anions both complex with copper and zinc (10).

We also became interested in fluoride complexes in consequence of the Handbook. We investigated some organic fluorides and found two complexing agents with magnesium and manganese, which inhibited alkaline phosphatase. By chance we found that histamine forms chelates with a series of heavy metals (copper, cobalt, nickel, and zinc), which we used immediately to investigate copper metabolism in the beating heart. Also, the previously mentioned storage of copper, manganese, and magnesium in the surface of heart muscle fibers was found. Soon we could give a complex constant for copper binding with tissue constituents. The results were lost in 1945 when my last luggage was burned during the great air attack on Dresden.

What interested me still more was the finding that Me-histamine formed two dissociation stages. That opened up the possibility of formation of ternary complexes. We had already observed the first sign of such a complex with protein, but in later research with Höbel it was proved conclusively although, as in the proteins investigated up till then, without firm bonding.

I have laid special emphasis on these experiments because the problem of fixation and release of pharmacologically active substances in the tissues is not yet satisfactorily solved; for example, the binding of histamine to heparin in the mast cells is not firm (Werle). With ternary complexes the following possibility exists. When a ternary complex exists in the cell for instance, as with copper, cobalt, zinc, or nickel, histamine is immobile. As soon as a substance arises in metabolism which forms a more stable complex with this heavy metal, then histamine will be set free and can fulfill a physiological function. But this is only one example and exactly the same can happen with thyroxin, adrenaline, insulin, etc. If one wishes to intrude into the mysterious realm of the structure of tissues, then one must piece together the structure in space out of an immense number of such small fragments, exactly like the analysis of a complicated organic molecule. Further research in Breslau had to be abandoned incomplete. With the experiments on the toxicology of explosives (the important results were lost), the ques-

tion of whether one could protect the liver against poisoning became of vital interest. We found a suitable drug in *Carduus marianus* and wanted to proceed with its isolation. This was later accomplished by Vogel in the firm Madaus, Cologne, and a useful medicament was introduced. All the wearisome work of building up the Institute for ten years and all the maturing research results were abruptly annihilated in the last phase of the war.

We will omit the following very difficult years; the flight, the separation of the family in three different places and the loss of our entire property, including clothes. In the following years until 1948 I busied myself as far as possible with mathematics until on 3rd March 1948 I came to Heidelberg and in the Surgery Clinic, through the friendship of K. H. Bauer, had the use of two unequipped rooms as laboratories, at first without technical assistance. A revision of the volume on the inorganic anions and completion of the literature survey was made possible with the help of America House. During this time also I wrote a more natural philosophical book "Die Prinzipien des Lebendigen." I began with the single hit theory of radiation. It seemed to me that in all later deductions, the fact of regulation in this very place was continually neglected. In my cogitations, the idea of harmony on the various levels was introduced and the postulate formulated that disharmony in the cell system is necessary to enable development and adaptation. The idea of the possibility of two hits, which in a short time interval struck very close together, could not be confirmed by experience, but on one point the later development came near to my deduction, in which the size of the target changes with the preliminary conditions.

Then I used my time doing clinical pharmacological tests for which I sat at the hospital bed daily for several hours, making measurements. A series of publications, also a monograph on hydergin as a medicament to improve circulation in local pathological conditions, emerged from these experiments. At this time, in the neighboring Max-Planck Institute for Medical Research, under the direction of Professor Bothe, the cyclotron was again put into working order. It was then possible for us to produce radioactive isotopes ourselves, as far as the strength of the cyclotron went (15 to 20 Mev). I carried out the isolations and at the same time, in Bothe's Institute, I learned the methods for measuring radioactive substances from the beginning. All these projects led to a continuation of the Breslau research on the surface of heart muscle fibers with the aid of radioactive-labelled pyrophosphate and phosphate and also with dyes. The circumstances seemed reasonably good and much was planned. I had almost forgotten that I, exiled from home, had a wife and three children who lived in Hamburg under straitened circumstances. As a permanent civil servant, I could expect a salary of only 540 DM per month from the government. As a basis, that would perhaps have sufficed had it not been for a regulation that extra earnings had to be deducted from this salary. In addition, my laboratory was still completely empty, without even primitive apparatus and without a personal budget at

my disposal. Therefore I was compelled, in order to proceed, to take over industrial work, renouncing any state salary so that the family could move to Heidelberg, as they did one and a half years later. We could then begin to procure our furniture, clothes, linen, and books. That I could not pursue purely theoretical projects is understandable and so my whole field of research was narrowed. One could not expect to be paid for working on mathematical formulae. Mathematical work makes sense for a pharmacologist only if he knows beforehand that a secure job can be guaranteed for a long time. When I began it in 1929, I could foresee nothing.

The themes that occupied me during the period from 1948 to 1958 are given in the following enumeration with their respective motivations.

(*a*) I received a small stipendium from the Strebel foundation for cancer and scarlet fever research. Therefore, I was compelled to work on cancer, which until then had not lain in my field. Indeed I had tried in vain to demonstrate a carcinogenic substance in roasted coffee. The early experiments were directed towards the isolation of nucleic acids from various vaccinated tumors under the action of cytostatics. But these experiments were not continued because finances ran out. In 1948, I obtained a series of substances from industry which were used in the treatment of wool fibers. First, we found the weak acting hexamethylolmelamin, later trimethylolmelamin which at the same time was discovered by Walpool and others in England. We made various investigations especially on the behavior of the cell nucleus in Ehrlich mouse ascites tumor, and also worked on its inactivity during longer treatment (research with Staib). When administered to humans in a series of experiments with several tumors they were found effective but very slow, although with only minor side effects. We could not continue these experiments further.

(*b*) While in Breslau, we had begun experiments with fluorine in collaboration with the dental clinician Professor Euler. In Germany, fluoride was known only as a rat poison. After a report at the dental congress in Wiesbaden in 1949, I suggested using fluoride in tablets for children. A memorandum was submitted to the "Hessischen" government but its publication was withheld by intrigues. However, I had at least patented a fluorine-containing toothpaste. The sale of the patent gave some money, part of which provided better equipment for the laboratories. After that we went ahead, together with Professor Ritter, to determine the distribution of fluorine in various enamel layers and found, by treatment with toothpaste, higher amounts of fluorine in the outer layers. These experiments were later continued and improved upon by Brudevold. We had spent much time on fluorine analysis and wanted to begin a survey of the fluorine content of the water sources, which in Germany had not then been done. Expenses were not granted because we were not in an official position, so the project had to be abandoned, as the analyses were too costly for us. We returned to our research in collaboration with Professor Ritter, using radioactive calcium

as the test substance to investigate metabolism in the growth of teeth in vivo.

(*c*) In the clinic, since we were treating patients with thyroid disease, we constantly had radioiodide at hand. It was used not only for treatment but also to investigate other problems; testing of medicaments acting on the thyroid, preparations of spurge (not published) and others such as atebrin. On this point, I had previously been interested in the behavior of the trachea with regard to the excretion of iodide. It was concentrated in the bronchial secretions, by an active transport mechanism, which suggested that possibly a new method of testing expectorants could be developed with it. On this theme very little work had previously been done; the best was by Boyd, whose method we partially followed. That is a topic most pharmacologists avoid because the method is wearisome and unpleasant. However, that is a poor reason for not working on such a project. There are some who firmly believe that only mitochondria or microsomes and perhaps even receptors are worth working on, Contrary to this, I have taken advice from Goethe: "According to our advice everyone should keep to his original path and should not be impressed by authority, be harrassed by general conformity or be carried away by fashion." I am pleased that I had been encouraged in this way by Straub and Heubner. Thus, we continued this project in the important research by Höbel. A short time ago he developed yet another preparation from the trachea, which he has examined in minute detail. With it one can follow the transport mechanisms very well. Iodine transport in the trachea was clearly found to be different from that in the stomach and thyroid. So also are the actions of perchlorate and thiocyanate, a theme that ties up with older research work extending over several decades. That is what Hackental worked on.

In 1950, the editing of the well-known Handbooks of Experimental Pharmacology was assigned to me by Heubner. As Editor I came in contact with Alfred Farah, formerly of Syracuse, with whom a close friendship has been formed after many years of working together in harmony.

At that time Handbooks were frequently deprecated. The reviews were modern but some colleagues were of the opinion that the Handbooks grew obsolete too quickly. On that point it should be noted that the reviews are often very superficial and sometimes more of a literature survey. In spite of this, I would not wish these reviews to be dispensed with.

A Handbook of Pharmacology brings together, at a certain point in time, a whole theme from many points of view and sometimes one can even omit looking up the original papers. Concerning its going out-of-date, one should note that in pharmacology, at various times, different groups of compounds will be worked on and tested, and perhaps will again become interesting after several decades. Then one can always find a great deal of information in old Handbooks, for instance, derivatives of quinine, pyrazolone, cocaine, local anaesthetics. That becoming obsolete does not happen so quickly depends also on the fact that pharmacology has been using isolated

organs continually for almost 100 years. In any case, the results give a lead and still today form a basis. Also, as Goethe asserted, in such encyclopedias, the mistakes will be remembered rather than forgotten as they deserve. Every Handbook article should be appreciated because it demands a great deal of self-denial. To do experiments is certainly more interesting, but such surveys are equally necessary because the work can be used in a thousand different ways. It stimulates new approaches and prevents the neglect of industrious work that would otherwise have to be repeated. Such literature surveys also belong to the great realm of the sciences. Writing reviews does not demand great knowledge but even the best research worker should write articles for the Handbooks. Such volumes in the Handbook of Experimental Pharmacology like those by Koelle, Bacq, Ussing, Berde, Jungmann, Erspamer, Graffi, Herken, and others seem to me to be of lasting value. I see a time coming when a prominent worker could be asked to revise such a Handbook because of his great experience and knowledge, for example, like the work undertaken by Brody. Because I am convinced of their worth and importance I have spent a great deal of time on them. Above all, the experimental production of disease in animals seems to me to be a necessary aid in research and so I have taken over the really laborious job of editing these books, even if reluctantly. I do not believe that one can achieve the same results with computers.

When I worked in the hospital, I also undertook the testing of various substances on patients (e.g. dibenamine, hydergin, polamidon, catechol amines, and arecoline). Although I finally held a Chair in Clinical Pharmacology, I could not be very effective because of a lack of co-workers, and I was really happy when finally, in 1958, I could take over the Direction of the Pharmacology Institute as successor to Eichholtz.

I came to an Institute in which most of the equipment necessary for my field of research was either lacking or obsolete. The structure was erected on the 500 year old foundations of an old monastery. The building itself was constructed in 1861 at the time of Helmholtz, who in those days also had his apartment there. A new building was planned for 1952 or 1953, during the time of Eichholtz and Fleckenstein. That the building was not erected was advantageous, for according to the plans, it would not have been sufficient. However, all applications for improvement were refused by the administration with the excuse that they were not worth while on account of the new building. I objected to this argument and by perseverance I succeeded in considerably augmenting the number of usable rooms. Slowly, it was being discovered that the prevalent neglect of science since 1914 should not be continued if we did not want to lose completely our former high prestige in science, with all the consequences for industry and education of students. But the investment of money in science was promoted very slowly and soon came to an end because of financial difficulties. For example, the animal house was in an indescribable condition. We did long-term animal experiments during which numerous epidemic infections were contracted, for in-

stance, once in the course of three weeks about 500 operated guinea pigs were destroyed. There were the application for planning a new building, detailed plans, refusals because it was too big and too expensive, new plans by the administration that were a little cheaper—and so it continued for six long years. When it came to the actual building; it became the most expensive animal house that ever was built, if one adds on the time wasted by Assistants and myself in repeating infected animal experiments, loss of working time, etc.

In those years, money was granted to modernize the apparatus of the completely out-dated Institute. Of course, I paid special attention to the work with radioisotopes and an ultracentrifuge, freezing centrifuge, spectrophotometer, electrophoresis apparatus, and good balances were procured. I only mention these things to indicate that previously they were nonexistent.

Until then, my course of life had lacked continuity; always new situations arose, new themes were taken up—had to be taken up as money was obtained from industry—and finally they became interesting and challenged me to continue. Thus, in the Institute there were many lines of research in progress. A series of projects by Assistants who worked almost independently ran side by side. Thus, Priv. Doz. Dr. Ellen Weber's section worked on thrombocytes and their metabolism. That seemed to be a promising project with simple structures. Greatest importance was placed on measuring both the chemical and histological effects in parallel, as in Breslau.

Hackental worked on perchlorate metabolism with ^{36}Cl-labeled compounds. These experiments followed logically to a transposition to bacteria and expanded to nitrate (which was already presented basically in my book on the pharmacology of inorganic anions). Besides studying the metabolism of the trachea, work on binding of ternary complexes was also pursued by Höbel and Lippert. I was very disappointed that problems arising from a short publication by me after the war were taken up by others from various aspects without my being able to participate for many years. Since 1958, we have done many experiments, the results of which will shortly be published.

I have followed the principle of taking on industrial work occasionally for several reasons. Assistants could thus come to grips with practical problems and learn methods. Otherwise that would be done in a pharmacology course but until then there was none in Germany. Professor Schmier held such a course in my Institute for small groups of 10–15 students. There was not enough space, technical assistance, or money for all the students to take this course. Some money was provided by industry which permitted investigation of antipyretics and their combinations, flavinoids, etc. In addition, this money was greatly needed to supplement the scanty budget and the meager assistants' salaries. This is the way it was used in other Institutes also.

Later, on behalf of the Government, we worked on fog, its deposition in the respiratory tract and also its resorptive action. The experiments also forced us to design and build new apparatus employing the laws of the flow of gases. The themes were too diverse to conform to our earlier accomplishments, but we had the advantage that the staff of the Institute also learned about many other methods and problems. Every two to four weeks relevant divisions had to report on their results. At these meetings there was discussion and mutual stimulation so that the possibility of collaboration on a special subject was established. Three of my Assistants were able to qualify.

On April 1, 1968 I became an emeritus Professor. I was happy that now all the purely theoretical themes of work could be undertaken. Through the pressure of various obligations, lecturing, examinations, medical reports and meetings, these had been neglected. Michel de Montaigne believed that it represented an arrogance to maintain the world by one's self. There is nothing further from my mind. But many Germans have been stricken with such a destiny in life and so the continuation of their work was interrupted. And so to finish, I would like to add a quotation by the same author: "I cannot base my life's records in achievements. Fate has made them too inconspicuous. I base them on my thoughts and humour".

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