

**MY BIOGRAPHY**

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To begin with, I want to thank Oakley Ray for asking me and for encouraging me to write this autobiography. My special thanks are due to my friend Thomas Ban for making me feel that this would be a worthwhile endeavor. Because of their efforts I had the pleasure to review and relive some of the events and happenings of my long life. It made me realize how fortunate I am in being alive, in being in good health and in having the means and attitude to fully enjoy these gifts.

I was born in Pilsen on June 25th, 1913. Pilsen, known for its beer, is located in the western part of Bohemia which, at that time, belonged to the Austrian-Hungarian Empire. On October 28, 1918, soon after the end of the First World War, The Czechoslovak Republic was founded. I remember to this day watching from the window of our apartment the parades taking place in the ancient town square of my native city. I enjoyed listening to the marching band of the Czech Army and I was frightened by the violent behavior of some participants of the parade toward some of the onlookers who, as it was

explained to me, were considered to be in sympathy with the old regime.

I soon learned that the man in the street blamed the German speaking people for all the problems and inequities that came to light after the establishment of the Czechoslovak Republic. Any German speaking person was considered an enemy and was made to feel unwelcome. This became a big problem to me because of the differences in the cultural background of my parents. Although my parents spoke Czech and German equally well, they came from different parts of the country. My mother was born in Kolin which is located near the central area of Bohemia where the influence of German speaking neighbors was not so strongly felt. My father, on the other hand, grew up in Pilsen, which was closer to the border area and where before 1918 more than one half of the population was German speaking. When I was in elementary school it became quite clear to me that there was a generally hostile feeling toward German speaking people. Often I felt that they suspected me of being a Czech

speaking German.

My problems were further complicated by my deafness. I was not clearly aware of my impaired hearing until my late fifties. What I knew since childhood was my inability to get the meaning of off-hand remarks spoken rapidly. People erroneously believed that my inability to respond to these comments in an appropriate manner was due to a lack of knowledge of Czech. I had a similar problem with English. A long time after I could read and speak English as well as native born Englishmen, I could not get the meaning of what was said when the message was delivered rapidly and in an off-hand manner. For me to understand the speaker, his message had to be clearly enunciated; he had to speak directly to me and he had to speak slowly. I attributed this inability to my lack of complete command of a foreign language. I am now convinced that it is due to my being deaf. This deficiency cannot be completely counteracted by wearing hearing aids, which, in essence, just increase the volume of what is being said. Deafness, on the other hand - or the deafness from which I suffer - is not so much

the inability to hear as it is the inability to decipher the meaning of what is being said. I can hear the sounds that the speaker is making, but have difficulties in getting the meaning of his message unless he delivers it slowly and enunciates carefully and clearly.

Few people realize what a handicap it is to be deaf. You cannot get the meaning of casual remarks, and you are considered impolite if you do not respond, or annoying or stupid if you ask "What did you say?" One wonders how many so-called retarded people are just deaf. So please be patient and understanding with those of us who cannot make out what you have said. But when you come right down to it, we are all deaf, perhaps to different frequencies or different problems. This is a shame, because deaf people cannot participate and what is there in life unless you are part of it -- you participate!

The man who impressed me most during my early youth was Thomas Masaryk, the founder and first President of the Czechoslovak Republic. Masaryk was born in 1850, the son of a coachman in a village in Moravia, a province adjoining eastern Bohemia. Somehow

he managed to get educated and in due course became Professor of Philosophy at the University of Vienna and a representative for Bohemia in the Austrian-Hungarian Parliament. It was always a puzzle to me how he managed to become an accomplished and wise politician and philosopher having grown up on an isolated farm and going to school where in all probability there was only one teacher and one class. There is no question in my mind that we all flourish to a larger or smaller extent with support, stimulation and encouragement. Masaryk must have been one of the rare persons able to overcome almost any difficulty to acquire knowledge about problems and situations that interested him. I greatly admired him for his determination to succeed in worthwhile endeavors and for his courage to champion unpopular causes. The latter became quite apparent in two prosecutions in which he got involved early in his career. In the first he successfully defended some Jews wrongly accused of ritual murder. In the other he studied some Czech manuscripts purporting to show how advanced Czech learning was in the fifth century A.D. and

proved them to be forgeries. Masaryk's motto was "truth will prevail". When he retired as President, Czech freedom and independence lost its most effective advocate. When Masaryk died in 1937 I felt that the Republic would not be able to maintain its independence for very long, and I started making plans to emigrate.

But I am running ahead of my story and want to say something about going to school in Pilsen. All schools in Czechoslovakia were state schools during the period I attended from 1919 to 1937. My mother, who was very concerned about education and wanted the best for me, sent me to the "Teachers College". At this institution the pupils served as subjects for the student-teachers to learn how to teach.

As a result of this we never had a teacher for any length of time. We found that amusing, but it deprived us of the opportunity to form a personal relationship with our teacher. To learn that such an attachment was possible was postponed and I feel that I have missed something important because of it. I feel that we learn more effectively from people we love and admire, and the development of a

caring relationship takes time.

During the fifth grade when we about ten to eleven years old we took a written entrance examination to high school. Those who passed the examination could, if they wanted, enter a gymnasium, real gymnasium or technical high school for eight years, and upon graduation enter a university or engineering school. Those who did not pass or chose not to take the examination went to a "citizen's school", business academy or school of crafts. I remember to this day the first school day in the "Realni Gymnasium", the Czech name for high school. Too many elementary school pupils apparently chose and succeeded in passing the entrance exams of this school, about 240 to be exact. We were informed that there would be four separate classes for the first grade, each with about 60 pupils. We were also informed that the school had the facilities to graduate just about 60 students, those with the best overall grades. Most of the remaining 180 would fall by the wayside before the end of the fourth year. The director of the school encouraged all that did not have a deep desire



for learning and hard work to leave and finish their education in a citizen's school. I stayed on and greatly enjoyed myself, particularly when classes became small after the fourth year.

I liked going to the gymnasium. The subjects were interesting and the examinations fair. I was especially fond of Latin which we had every day and twice on Thursday. We read Ovid, Horatius and others and I greatly enjoyed their re-telling of the Homeric tales. We learned enough Latin to circulate among us and read after hours some of the classics such as Ovid's "Ars Amandi" (the art of making love), and considered these as the "How To" books of our youth. Upon graduation I decided to enter the German University in Prague.

I am trying to recall why I chose to become a doctor. Financial consideration did not play any part in this as education in Czechoslovakia, as in most other European countries, was freely available to all able to pass the prescribed state examinations. My father had a successful business and wanted me to join him, but I did not want to enter a profession that would have anything to do with

buying and selling. I decided to study medicine as I felt that the life of a physician would bring me closest to and help me understand the great mysteries of life such as birth and death, suffering, sex and love. Until that time all my education was in Czech. There were two medical schools in Prague; one Czech and the other one German, both claiming direct descent from Charles' University. I must have chosen the German University because I wanted to get away from what I considered the narrow nationalism of the Czech institutions. In any case, I am glad that I had the courage to make a new start. By switching over into a new environment I lost most of my old friends and learned that it is possible to thrive in new circumstances. I lived in Prague in a rented room and greatly enjoyed my new life in the big city. I perfected my German by attending lectures and found the direct and factual way in which the subjects were presented to be fascinating. I learned that one of the lecturers in physiology, Prof. Richard H. Kahn, gave a course in experimental physiology that was limited to twelve selected students. Taking this course did not acquire

credits, and only students personally selected by Prof. Kahn could take it. I tried very hard to be accepted because I was fascinated by Prof. Kahn's personality. During his lectures I got the feeling that new and important insights were being revealed to me. He also made it clear how little is known and how important and enjoyable it is to do research. I was accepted to the course and Prof. Kahn personally taught me not only how to carry out experiments on animals, but also how scientists work and think. I felt that I should start doing research on my own and asked Prof. Kahn to help me in this endeavor. That was in 1934 when I was twenty-one years old during my second year at the Medical School. The subject I wanted to study was the identification and characterization of hormones of the adrenal gland. At that time only epinephrine had been isolated in pure form, but there were many articles describing other substances present in extracts from adrenals that possessed unexpected and fascinating properties. Prof. Kahn considered the project too difficult and suggested I start with something simple. There was interest in finding routes by which

to administer insulin other than injection. To study insulin absorption after inhalation of an aerosol did not appeal to me. I was aware, however, that Prof. Kahn had some ovariectomized rats available and it occurred to me that it would be interesting to compare the effect of the follicle hormone given by the subcutaneous route with that obtained after intravaginal administration. The effect could be easily evaluated by taking vaginal smears. The presence of fully hormified epithelial cells (oestrus) was indicative of the full hormonal effect. Prof. Kahn agreed to the project which in due course led to my first publication entitled "The Especially High Effectiveness of the Follicular Hormone After Vaginal Administration". It appeared in German in the journal "Klinische Wochenschrift" in November 1935. I was proud that my paper was accepted in this prestigious medical journal and happy that it attracted a lot of attention as judged by the requests for reprints and correspondence from interested readers. This paper, together with a second paper which appeared in the same journal in October 1937, established that the follicular hormone acts

directly on the cells of the genital tract and that this route of administration is more effective than the parenteral route.

While this work was in progress a close personal relationship developed between Prof. Kahn and me. Two or three times a week at the end of the day I went to see him at his office at the Institute of Physiology. We talked about science, politics and wisdom in abstract terms without ever mentioning particular views. He was a wise and decent man, and he greatly influenced my life. He never gave me advice; he never complained; and he never talked badly about anybody. He never told me what to do. I never had a meal with him nor was I ever invited to his home. Yet he had a more profound influence on my life than most other people I have met. I owe Prof. Kahn a great debt of gratitude. Without ever saying it he made me feel that the only pursuit worthy of a gentleman is to try to find out how the universe works, which is what science is all about. He also made it clear to me, without ever saying it, that one has to be practical and that at times it is necessary to manipulate to some extent forces in

this imperfect world in such a manner that one can attain one's ultimate objectives.

During 1935 another important thing happened to me: I met my future wife, Bozena Jahodova. She was a nurse in the Department of Internal Medicine in Prague where I experienced my first contact with patients. She impressed <sup>e</sup>my greatly. She was always immaculately put together in clean and well pressed attire. She always had a cheerful expression and invariably was kindly, helpful, understanding, and patient with patients. I fell in love and Bozena soon became my true love and best friend. I soon found a way to become financially independent - or so I thought I did - so I rented a modern apartment and persuaded Bozena in 1936 to resign from her job and move in with me. She did, and we both greatly enjoyed our life together. These were exciting days. Hitler was asserting his power, and it became clear to me that it would only be a question of time before he would occupy Czechoslovakia. I also felt that I would not want to live in a country occupied by the Nazis, not only because I knew they

would not approve of my genetic makeup, but also because of my liberal, left wing humanist outlook and point of view which I never made a secret. These were also busy days. I was a good student and seemed to pass most of my examinations with high honors. I did independent scientific research that seemed to attract worldwide attention; I lived with the woman I loved and admired; and I managed to make more money than I needed. All these activities kept me so busy that I had little time left to worry about what was going to happen to me and my family in the event of war or Nazi occupation. But I did not forget completely. I persuaded my father to make arrangements with his younger brother who lived in Cleveland, Ohio to arrange for us to receive affidavits so that we could obtain visas to emigrate to the United States. My parents and my brother and sister, Bożena and myself all received emigration visas and I started taking English lessons, since it was one of the languages which was not taught at school.

As I got to know some of my fellow students at the Medical

School, I noticed that many of them got quite concerned about the forthcoming examinations. In Czechoslovakia education was free, provided you had passed the final examinations at the Gymnasium. All you had to do to obtain a medical degree was to successfully pass eighteen examinations called "rigorosa". Each examination could be retaken only twice. After the second failure in any one of the rigorosa, studies could not be continued and one was discharged from the University. The rate of failure was quite high and, in my opinion, due to the large size of the classes (there were 400 students in my semester), and the difficulty in establishing a close contact with the teacher. Another reason for the high failure rate was the mistaken belief of many students that they would be asked at the examinations only about subjects that had been brought up and discussed during lectures. This, of course, was not the case. The failure rate was highest in pharmacology, and I conceived the idea that there might be a demand for a concise summary of the essentials of pharmacology that would simplify the preparation for the examination. The idea to



study pharmacology appealed to me because at that time I considered pharmacology, the knowledge of how to use drugs, the most important task confronting the future physician. At that time, in 1934, I was still a medical student and decided to spend the summer vacation of July and August studying pharmacology. I purchased four different textbooks, read them from cover to cover, annotated them, and summarized what I thought were the most important subjects in the field under twelve headings such as the pharmacology of the central nervous system, the pharmacology of the autonomic nervous systems, etc. I approached the owner of the University Bookstore ( his name was Tozicka) who typed the document which, incidentally, was quite lengthy, comprising 119 single-spaced, legal size sheets. He sold this mimeographed document under the name "Scripta Pharmacologica" without disclosing my name for the sum of several hundred Czech crowns, which at that time was quite a substantial sum. The royalty I received from the sales of the scripta enabled me to take my late wife, who at that time was my girlfriend, on a wonderful trip to Dubrovnik

in Yugoslavia and Tirana in Albania. This was the summer of 1935, and I still remember with pleasure the interesting and enjoyable time we had.

I should say that at the time the scripta were published, I had not yet taken the rigorosa in pharmacology and was concerned that Prof. Starkenstein, who was the examiner, would not pass me. I am saying this because it was felt that the existence of my scripta substantially decreased attendance at the Starkenstein lectures and Starkenstein mentioned on several occasions that should he ever catch the author, he would treat him appropriately.

The writing of the scripta had a profound influence on my life. By trying to learn what pharmacology was all about and forcing myself to write it down in an easily comprehensible form, I became well acquainted with the subject. Although I lost interest in the field soon after 1935, my knowledge of pharmacology came in handy when I started working with mephenesin in 1945 in connection with my penicillin studies. I recently found a copy of the mimeographed

scripta among the papers I have carried with me since I left my native country and deposited them with my reprints and other papers at the American College of Neuropsychopharmacology at Vanderbilt University in Nashville, Tennessee.

By the end of 1935 I felt that there were no projects that I would like to tackle at the Institute of Physiology. Prof. Kahn, who knew of my interest in microbiology, suggested that I approach Prof. Ernst Singer at the Institute of Hygiene. Prof. Singer was a kind and understanding man. He took me on, let me work in his laboratory, and personally taught me the laboratory techniques used in bacteriology, virology and immunology. He suggested that I read up on bacteriophages. This is a family of viruses that infect and kill bacteria. I reviewed the literature on these fascinating agents and worked out and published a method for the isolation of specific phages that could be used in the treatment of bacterial inflammation of the bladder. The method worked but it was cumbersome because it required the preparation of a specific phage for each patient which then had to be

instilled into the bladder. This treatment was quite effective but was abandoned in the late 30's when the effectiveness of the sulphonamides in the treatment of cystitis was recognized. It is of interest that the therapeutic utility of bacteriophages is now being reinvestigated because of their effectiveness in antibiotic-resistant bacteria.

The Institute of Hygiene of the German University of Prague became - improbable as it sounds - one of the most important centers for research on Rocky Mountain Fever. The test most widely used for the diagnosis of this disease was discovered by a former chairman of the Institute, Prof. Weil, early in the twentieth century. Prof. Prowazek, another chairman of the department was, together with Dr. Ricketts, co-discoverer of the agent causing the disease which was named *Rickettsia Prowazeky* to recognize his contribution. Prof. Breinl, who was chairman at the time I worked there, together with Prof. Singer, worked on the development of a vaccine for the prevention of the disease, utilizing feces from infected lice as the

starting material. Prof. Breinl died from a laboratory infection of Rocky Mountain Spotted Fever during my stay at the Institute.

However, Rocky Mountain Spotted Fever was not the only disease studied at the Institute. Prof. Singer's main interest was in Nagana, the African Sleeping sickness caused by trypanosoma brucei.

When I joined Prof. Singer in 1936 it became my first assignment to keep this beautiful parasite alive and virulent. As trypanosomes cannot survive on artificial media, it was necessary to keep them alive in living mice. Each week I had to bleed mice at the peak of their infection and to inject their blood which contained millions of trypanosomes into another group of healthy mice. This had to be done before the trypanosomes killed the mice which usually happened around the 10th day of the disease. I have rarely seen a more fascinating spectacle than the living trypanosomes under the microscope, lively moving around in a drop of blood.

I wanted to develop a treatment for sleeping Sickness and thought that short wave radiation, which was becoming popular at that

time could be utilized in this context. The basic idea was to find a substance that would be selectively taken up by the trypanosomes and sensitize them to the effects of short waves. I could not handle such a project by myself so I was glad that my friend and colleague, George Brecher, was interested in the project. Prof. Singer was agreeable to his joining the laboratory and his presence was particularly valuable because of George's deep knowledge of physics and mathematics which played an important part in this project. Machines producing short wave radiation of considerable power became available at that time. What we needed was a non-toxic agent that would selectively accumulate in the trypanosomes and make them sensitive to the short wave radiation. Certain metals appeared to have such properties because of their ability to focus and locally intensify the electric field. Singer had also previously shown that various metal containing compounds are selectively taken up and retained by trypanosomes. We carried out numerous experiments with gold containing compounds which accumulated in the trypanosomes and under

optimal conditions of short wave irradiation substantially reduced their number, but we were never able to achieve survival of all infected animals. We also felt that the general resistance of the animals was reduced because our treatment also destroyed part of the reticuloendothelial system as many cells belonging to it also were taking up our gold compound. Nevertheless, we published our results as we felt that the basic idea, which could be called the "microwave oven approach" might have some merit in other conditions utilizing other parts of the spectrum with appropriate sensitizers.

The time spent at the Institute of Hygiene was beneficial to me for several reasons. It taught me microbiology and immunology by making me do all the routine tests carried out in laboratories. It also gave me the opportunity to carry out independent research and to become a friend of Dr. Singer with whom I kept in touch and remained close all my life.

Toward the end of 1936 I had to drastically limit my scientific activities and start studying seriously for the final medical

examinations. I passed most of them with flying colors and did not have to repeat any. I was awarded my medical degree in December, 1937.

These were exciting and tense times for Czechoslovakia. Hitler was gaining power and I felt that it would only be a question of time until the country would be occupied by German forces. I also had to decide what I wanted to do with my life. I did not want to become a medical practitioner because I felt uncomfortable about charging fees for services that I strongly believed were the birthright of every sick person. I was interested in doing research and took a position as a bacteriologist at the National Health Institute in Prague. The head of the division was Prof. Jaroslav Drbohlav, internationally known because of his success in cultivating for the first time *Entamoeba histolytica*, the cause of amoebic dysentery. My general assignment was to establish a National Collection of Type Cultures. I was given two technicians to help me with this task and was greatly gratified to know that for the first time in my life I could delegate to others some



of the less important activities, such as cleaning glassware and sterilizing instruments. Although I was not responsible for the diagnostic laboratory next door, I noticed that the bulk of samples tested by them were from outbreaks of diarrhea. There were problems in identifying the different types of paratyphoid microorganisms that occurred in the feces of these patients and I took it upon myself to duplicate the work of Kaufman and others by preparing specific antisera for the various O and H antigens of the Salmonellas. These antisera could be used in the identification of Salmonellas which is important in tracing the sources of diarrheal disease. For this work I was awarded the Czechoslovak National Prize for Scientific Research on October 28, 1938.

By the end of 1938 it became clear to me it was time to start seriously thinking about emigration. I was fortunate in having an uncle in Cleveland, Ohio who was willing and able to make the arrangements so that immigration visas were issued to my parents, my brother and sister, and to my girlfriend and future wife Bozena and

myself. When I learned on March 14, 1939 that the German Armed Forces started occupying Czechoslovakia, I married Bozena the following day and boarded a train to Rotterdam the day after that. We had prepaid tickets from Prague to Cleveland which included the Atlantic crossing by steamer. We were permitted to take luggage but could not take any money. We did not worry about that and boarded the train in good spirits. After an overnight train ride we arrived on the Dutch border and were ordered to leave the train with all our belongings. We found ourselves in a Dutch village called Oldenzahl. We were informed that we could not continue our journey because all American visas granted to Czechoslovak Nationals had been declared invalid and cancelled. The inhabitants of Oldenzahl put us up for the night in their own homes and let us use their phones to make whatever arrangements we could to find a country that would accept us. It was made clear to us that those that could not find shelter within a week would be sent back to Czechoslovakia. I called everyone I could think of for advice and help. My friend, Richard Spitzer, with whom I went

to medical school and who then lived in England put me in touch with the Quakers who provided an entry permit for my wife and myself, and by doing that saved our lives. We never learned the identity of the person who obtained the papers for us and guaranteed that we would not become a public burden. It was all done in the true Quaker way: silent help from the nameless to the nameless. I have been greatly impressed by the Quaker way of life and I am trying to follow their example.

After arrival in London we had a rough time. My English was not good and my total fortune amounted to twenty pounds that George Brecher lent me. These funds were sufficient to rent a room for a few days. We soon discovered that my wife was pregnant and were fortunate that the Jewish Shelter at the East Side took her in. This was wonderful and remarkable as Bozena was not Jewish and had no Jewish relatives. As for myself, nobody seemed to want me so I went for my meals to the Salvation Army and spent my nights on park benches. As a rule I was picked up by the police before midnight and,

as I had no home, was delivered to the Brixton Prison for the night. I did not mind this as long as I got "solitary". Unfortunately, most of the time I had to share a room with a hundred or so homeless people. I spent the days trying to find a job and learning English. At last the Czech Refugees Trust Fund took pity on me and my wife and had us admitted to a refugee camp in Broadstairs. This camp housed several hundred refugees from Czechoslovakia, Poland, Hungary and other occupied countries, and I became the camp's physician, working with and under the direction of a local doctor. We all received a small monetary stipend from which we had to provide for all our needs, including food. We organized a communal kitchen and had plenty of free time on our hands which we mostly used to learn English. This was greatly facilitated by Miss Griffith, a retired English teacher who organized a teaching program for us and entertained us for tea in her home. She was a kind, well-meaning lady that was not interested in politics, but strongly believed in the worth of all people. We all owe her a great debt of gratitude. People like her keep the world on an

even keel. They do not wonder about causes or purpose, but give help where they can and give it freely and unselfishly.

On November 1st my wife started giving birth. When, after ten hours, the baby showed signs of distress, nothing could be done because facilities for a Caesarian section were not available. The baby boy was dead at birth, November 2, 1939. To this day, more than sixty-one years later, I have not recovered from the pain I suffered. It became clear to me and Bozena right then that we must have children under more favorable conditions and we were fortunate to fulfill this objective after we came to the United States.

After the occupation of France in 1940, the Germans started shelling the coast of Kent from Normandy. The camp was broken up and my wife and I were moved with about twenty-five other refugees to a house in Kingston-on-Thames. By that time my English was quite satisfactory, and I was anxious to start working. This, however, was not possible because of government regulations. I spent my time reading medical journals discarded by the local hospital and by talking

with William Bradley, who was the government appointed warden of our hostel (the name used when referring to our habitat which was a kind of open-door prison). Bradley was a delightful person. About sixty-five years old, from modest circumstances, self-educated, wise, rational and proper. I was delighted to find that the person who was appointed to be my jailer shared most of my beliefs and attitudes. He felt as I did that all forms of violence were reprehensible, that no problem has ever been solved by wars, that there could be no God requiring our continued expressions of loyalty and devotion, that those in power would always try to decide what was right and would be more concerned about retaining power than in the well-being of those they controlled. At that time the bombing of London by the Luftwaffe was a nightly event and Kingston, being part of Greater London, got its share of attention. We soon found out that most injuries were caused by flying objects and that it was quite safe to avoid the indignities of air raid shelters by staying home while making sure that all windows were open. To be distracted from the noise made by the

exploding bombs, we listened to the BBC radio programs in which C.E.M. Joad, a philosopher, discussed with Julian Huxley, a biologist, the eternal questions of the meaning and purpose of life and the guidance we may receive from science and learning to lead the good life. When the programs were not available we read and discussed the introductions to the plays by Bernard Shaw. Those were memorable and enjoyable evenings. I miss Mr. Bradley, his comments, his insights and his humanity. He was a wonderful man. He made me feel that most civilized men feel as I do and that their views, in due course, will prevail. We just must not give up. Truth will prevail.

Another pleasant event that took place during our stay at Kingston was my sister Eva's visit. She somehow managed to obtain an entry permit to England as a maid and, as a result, was able to leave Czechoslovakia just before the war started. We became good friends. I had always admired her courage and good sense to adjust to new situations. She had the ability to enjoy herself under all circumstances. She soon found a delightful husband, a native-born

Brit of Italian parentage, with whom she started a lunch counter and later a restaurant which managed to prosper even during the war when foods were strictly rationed. I remember the places well, as Bozena and I had some of our best meals in their restaurants. They are still together, happily married for sixty-one years, enjoying their two daughters and grandchildren.

The shortage of physicians caused by the war brought about another event to which I had been looking forward: Czech physicians were permitted to practice in hospitals and research institutions. I succeeded in obtaining a position as resident at the Monsall Hospital for Infectious Diseases, a large 500-bed hospital affiliated with the University of Manchester School of Medicine. We had a busy time as most of the beds were occupied with acutely ill patients, and this entire load was handled by the Superintendent, his deputy and three residents. At that time (I believe it was in 1941 or 1942) there was an epidemic of diphtheria in the area. Many of the patients were infants and I remember admitting up to twelve on some nights. Most of the



infants were in toxic shock, displaying a "bull neck". Their chances of survival, we felt, depended on our ability to administer antitoxin intravenously. To succeed in doing this in an infant in shock is most difficult, even when recourse is taken to a surgical exposure of a vein. Many of the infants did not survive, and one of the most painful tasks I ever had was to inform the anxious parents.

Another epidemic that afflicted most young woman military auxiliaries was meningococcal meningitis, which was thought to be caused by the crowded conditions under which the young women were forced to live. This epidemic occurred before antibiotics became available, and was difficult to combat with the available sulphonamids and antisera. We also had many cases of polio and often needed all the eleven iron lungs that we had available. As a rule we also had two typhoid wards, many patients with tuberculosis, and a large ward with puerperal patients. According to a regulation in force at that time, it was necessary to move to an infectious diseases hospital any woman about to give birth or after having given birth who had a temperature

of 101° F.

I learned a lot at Monsall Hospital and found the experience most enriching. I learned how fragile human life is and how precious. I learned that there is no justice and that one cannot predict who will live and who will die. I also began to appreciate how little we know and how much there is to learn. I also began to realize that I am too sensitive a person to be a practicing physician. I was too deeply affected by the suffering of my patients and too angry about my inability to help them. I felt that I should go back to the laboratory and, in due course, was accepted as an assistant bacteriologist in the Public Health Laboratory of the West Riding of Yorkshire which was located in Wakefield. This was the diagnostic laboratory for the West Yorkshire area and performed routine diagnostic services such as the serodiagnosis of syphilis and typhoid and isolation of pathogens from the feces, blood and urine. I enjoyed involvement in this service and described several improvements in diagnostic methods for serological detection of syphilis and typhoid. I also isolated the feces of patients

in a small dysentery-like outbreak a paracolon organism which I mistakenly named Dysentery Wakefield instead of Paracolon Wakefield.

### Penicillin and Mephenesin

Having a fairly well equipped laboratory at my disposal reawakened my interest in penicillin. I was familiar with Fleming's paper of 1928 describing the almost miraculous antibacterial properties of the substance and was planning to work with it in 1938 when I was at the NIH in Prague, but did not get to it. In 1943 in Wakefield I heard rumors that extensive work on penicillin was being carried out at Oxford University under Dr. Floret's direction but had no access to it. I obtained a subculture of the penicillin mold from Sir Alexander Fleming and started growing it in flasks and extracting it by the published methods. These extracted penicillin as an acid and involved extraction from strongly acidified aqueous solutions into organic solvents. This resulted in very substantial losses of activity because of the instability of penicillin in an acid environment. My

idea was to extract penicillin as a salt at a neutral pH at which it was stable. I found that n-butyl alcohol in the presence of ammonium sulfate would almost quantitatively extract penicillin at a neutral pH and defined conditions to obtain a fairly pure product that appeared non-toxic and clinically effective. I could do all these things because I had the support of Dr. P.L. Sutherland, the Head of the laboratory, who gave me a free hand and established contacts for me at local hospitals.

I published my method of purification in Nature in 1944 and this resulted in job offers from drug firms interested in the manufacture of penicillin. I accepted a position in the British Drug Houses in London and started working there in 1945. I reported to Dr. William Bradley, a fine organic chemist. Bradley wanted to find a substance that would protect penicillin solutions from contamination with penicillinase-producing bacteria. These were gram-negative, non-pathogenic microorganisms that were present in the air. Glycol ethers were known to kill these contaminants but were of low activity.

Bradley's group prepared a series of glycerol ethers which I tested and found more active. Pharmacological evaluation indicated that these were on the whole non-toxic substances which, in large doses, produced profound paralysis of voluntary muscles.

At this point in time it was found that the best way to preserve penicillin was by freeze drying, which meant subjecting the frozen penicillin solutions to a vacuum until it became a powder and keeping the penicillin powder in the dry state. This was a more practical way which eliminated the need for antibacterial preservatives. I was, however, greatly impressed with the tranquilizing and muscle relaxant action of the substances and decided to investigate one of the compounds in greater detail.

The compound selected for a detailed study was a glycerol ether which, in accordance with the British chemical nomenclature, would be described as the alpha-beta dihydroxy-gamma-(methyl phenoxy)-propane. At present it would be called 3-(2-methyl phenoxy)-1,2-propanediol. The British Drug Houses trademarked the name

“Myanesin” to describe it. The generic name later assigned to this compound was mephenesin.

The first paper on this subject submitted to the just-founded British Journal of Pharmacology in September 1946 appeared in December of that year and pointed out in the second sentence of the introduction: “Administration of small quantities of these substances (the alpha-substituted ethers of glycerol) to mice, rats or guinea pigs caused tranquilization, muscle relaxation, and a sleep-like condition from which the animals could be roused. Larger doses produced ataxia, which was followed by paralysis. The animals did not react to painful stimuli and were unable to turn over when placed on their backs; all muscles were well relaxed and quite limp. Paralysis was followed by complete recovery. Excitement, tremors, twitchings or convulsions did not occur at any time after administration of the drug.”

The paper also described the unusual anticonvulsant action which is different from that of the barbiturates. Mephenesin was very

effective in counteracting strychnine induced convulsion and death, and was able to do so in small doses that did not seem to affect the animals in any other way. Hexobarbital, on the other hand, even in narcotic doses, was quite ineffective in preventing strychnine induced convulsions and death. When convulsions were induced by leptazol, hexobarbital was greatly superior to mephenesin in preventing convulsions and death.

I have described the paralyzing and anti-strychnine action of mephenesin at some length because they made a deep impression on me and convinced me that the drug had unusual properties different from those of the barbiturates and other central nervous system depressants. I felt that a clinical evaluation should be started without delay. After I satisfied myself that the drug is rapidly inactivated in the body and tolerated in fairly high doses for several weeks by rats and rabbits, I decided to have the drug evaluated for producing muscle relaxation during anesthesia. The drug used for this purpose in the late 1940's was curare. Curare in effective muscle relaxant doses

invariably paralyzed the diaphragm and caused respiratory arrest. I knew that mephenesin could produce profound muscular relaxation without affecting the diaphragm or respiration and thought this to be important. Clinical trials were arranged to see whether mephenesin could be used to replace curare preparations. To do this an injectable form was prepared using a mixture of propylene glycol and ethanol as solvents to overcome the low water solubility of mephenesin. This product was made available to a number of surgeons. It was irritating to the tissues and had to be administered by the intravenous route. While satisfactory muscle relaxation was obtained after doses in 10 ml of a 10% solution, the effect as a rule lasted only 20 to 30 minutes when additional amounts had to be injected. The mephenesin solution in some patients seemed to produce severe venous thrombosis at the site of injection. Myanesin injection also proved remarkably effective in the treatment of tetanus. However, the irritant properties of the solvents needed to prepare soluble mephenesin precluded its use in clinical medicine.



After the World War ended in 1945 I soon learned that my parents and many friends and relatives had died in concentration camps. I was pained and bitter, and decided not to return. My brother, who during the war had served in the Czechoslovak Division of the British Army, went back to receive our parents' property only to be deprived of it again three years later when the Communists came to power. Bozena went for a short visit and agreed with me that for us the best thing to do was to go to the United States and start a family. We applied for immigration visas which, thanks to the efforts of my uncle Paul, we received in June, 1947. At that time, two peculiar regulations were in force which did not make our trip any easier. The British regulation limited the amount of money one was permitted to export to a few hundred dollars. The U.S. Embassy informed me that the regulations in force at that time could issue visas only to immigrants who had no prearranged job waiting for them in the U.S.A. I did not, and we sailed to the U.S.A in October 1947.

I knew that Uncle Paul at that time was not prosperous and that

he could not support us for any length of time, but I did not worry too much. My publications on Myanasin attracted attention of several physicians in the U.S.A and I kept their reprint requests. As soon as we got to New York I contacted several of them, making it clear that I was now in need of a job. I was pleasantly surprised and greatly gratified by the warm response I received. Many of these people took it upon themselves to help me and to try to find a job for me. The reception I received was quite different from that I had in England when I was looking for a job in 1939. People in England were courteous but did not go out of their way to help me. It was quite different in America. I remember with fond memories and gratitude many people who took great trouble on my behalf right after my arrival on these shores, among these Irving Page, Director of Research at the Cleveland Clinic; Edward Schlesinger, a surgeon at the Presbyterian Hospital in New York; Carl Pfeifer, Professor of Pharmacology at the University of Illinois; and Harry Beckman, Professor of Pharmacology at Marquette University. All of these have

passed away by now. The man who helped me most at that time, and who is still very much alive, was my old friend George Brecher who by then was the hematologist at the National Institute of Health in Bethesda. He took the trouble to come to New York to welcome me and Bozena. At that time I knew nothing about the pecking order of American universities and was inclined to take the job with the best salary. George's gentle guidance and moral support steered me in the right direction.

I accepted a job at the University of Rochester Medical School at Rochester, New York. The job carried the title of Assistant Professor of Pediatrics and was funded by the national Foundation for Infantile Paralysis. I reported to Dr. R.P. Schwartz, who was Professor of Orthopedic Surgery and the administrator of grant money. I new exactly what I wanted to do. I wanted to develop a better Myanesin and Dr.Schwartz gave me a free hand to do so. I wanted a compound that would have the muscle relaxant action of Myanesin, but would be longer acting. I knew that as early as 30

minutes after swallowing a tablet of Myanesin, breakdown products of the drug appeared in the urine which gave Ehrlich's diazo reaction. It was necessary, I felt, to find out how Myanesin was broken down in the body so that one could design a molecule that would not be so rapidly degraded. This was a task which was beyond my knowledge of chemistry. I was fortunate to meet Dr. Richard A. Riley, a brilliant biochemist who identified the main breakdown product of Myanesin as its lactic acid derivative. This compound did not possess any Myanesin-like activity in the mouse. These results indicated that Myanesin is broken down in the body by oxidation of the terminal hydroxyl group. I concluded that longer acting products could be obtained by making the terminal OH group inaccessible to oxidation by blocking it. This was achieved by preparing the acid succinate of Myanesin which, as predicated, had an action of considerably longer duration than Myanesin. The product was shown to liberate Myanesin when incubated with liver homogenates. It was not thought worthy of a clinical evaluation because its intrinsic muscle relaxant activity was

no stronger than that of Myanesin. In an attempt to prepare compounds possessing stronger muscle relaxant action, Drs. V. Boekelheide and D.S. Tarbell, working in the Department of Chemistry, prepared a number of novel compounds containing a glycerol grouping. Some of these and particularly a 2-substituted-4-hydroxymethyl-1,3-dioxolane called Glyketal was about twice as effective a muscle relaxant as Myanesin and had a more favorable margin of safety. It should have been further evaluated, and I cannot remember why it was not.

While all this activity was in progress I decided to obtain a license to practice medicine in New York State. To obtain this I had to take the examination taken by all medical students after graduation. I accomplished that in 1948 when I was 35 years. In essence this meant that I had to retake all the examinations which were needed to obtain my MD at the University of Prague in 1937 when I was 24. After I obtained my license to practice medicine in the U.S.A., I was able to return to my researches with renewed energy.

I felt at that time that it would be a long time before an agent clearly superior to Myanesin would be found. I was intrigued by the results obtained by Schlesinger and others in spastic and hyperkinetic states after intravenous administration of Myanesin. I knew that the drug was orally effective in animals and I demonstrated the presence of Myanesin in my urine 15 minutes after taking a gram of the drug. That made me feel that a careful study of the effects obtained with Myanesin given orally should be carried out. I carried out electromyographic recordings in patients suffering from spastic and hyperkinetic disorders before and after the oral administration of Myanesin which dramatically illustrated the drug effects and published a report which appeared in the Journal of American Medical Association in June 1948. The study attracted a lot of attention and was widely reported in the press. E.R. Squibb and Sons, who marketed Myanesin in the U.S.A. under the tradename "Tolserol" vigorously promoted the drug which soon became their best selling product. I had patients coming to see me from all over the country. I

was doing well but I felt that this was the time to reevaluate my position and to formulate my plans for the future. What did I want to be? A university professor ending up with a chair in pharmacology, a practicing physician or a developer of new drugs working with or for a pharmaceutical firm?

I felt I needed a change although I was doing remarkable well at the university. Since arriving in Rochester at the end of 1947 I published or submitted for publication to peer reviewed prestigious journals such as Science, The Journal of Pharmacology and Experimental Therapeutics eleven publications within a year. I established successful collaborative projects with several clinicians and pure scientists and received several substantial grants to purchase needed equipment. However, much to my delight, my wife became pregnant and I felt that I had to take steps to give her some security in case of my death. I applied for a term insurance policy on my life but was rejected because of high cholesterol. (I put myself on a diet and eventually obtained insurance protection on reapplication). I could not

count on any help from my uncle and had to borrow money to be able to purchase a car and a refrigerator.

Much to the consternation of my many friends, I decided that joining the pharmaceutical industry would be best. My decision was based on the following considerations: I recognized that I did not belong in a university hospital because I was not interested in teaching. I wanted to develop new drugs and did not like to spend time writing grant applications and provide detailed accounting on how the grant money has been spent. I was primarily interested in applied research. I recognized then, and still believe, that pure research might be beyond my reach. Another reason I did not want a university appointment was the low salary, which at that time amounted to \$5,400 a year. I could not see any clear way how to increase it in a substantial way. I did not want to depend on the generosity of the pharmaceutical industry that was offering me stipends for the evaluation of their drugs. I did not want to spend my time and efforts in applying for grants to charitable foundations and I



did not want to practice medicine.

My reasons were that I strongly believed, and still do, that all people should receive the best available medical and psychological advice as a prophylactic and therapeutic measure, that this is one of the basic human rights, and that this service should be available to everyone free of charge and without respect to his social status or wealth. I noticed many medical students wanted to become physicians not because they felt a calling but because they wanted to become prosperous. I felt, and still do, that physicians should be paid a generous salary by the State and that their income should not be affected by the number of patients they attract. On the contrary, the number of patients any physician could look after should have an upper limit so that the physician would have enough time to spend with each patient. Such an arrangement would also make it possible for the physician to keep abreast of recent advances by attending graduate courses and medical conferences. At present, as is generally known, most physicians are receiving their post-graduate education

from detail men who understandably try to persuade the physician to prescribe the drugs sold by their employers.

Another reason I did not want to go into practice was the observation that those most in need of my services were least able to pay for them. Also I got too deeply involved with the problems of my patients to try to enforce the payment of fees. I let it be known that I was interested in a position in the pharmaceutical industry and was delighted to be approached by Carter Products, well known at that time for their laxative, Carters Little Liver Pills. The firm also had a small pharmaceutical subsidiary called Wallace Laboratories that sold dermatological products. At that time I was quite disappointed with the treatment I got from Squibb. There was no question that my clinical paper in the Journal of the American Medical Association made their product Tolserol a great success. They offered me a position but would not consider my financial participation in any new products that I developed. Other pharmaceutical firms who considered employing me also found my idea of receiving benefits

from patented products I invented unacceptable.

I was delighted when I was interviewed by Mr. H.H. Hoyt, who controlled the majority of the Carter Products stock and was the Chief Executive Officer of the firm. He wanted to know whether I thought it possible to develop a drug as good and successful as Tolserol. I felt confident that I could do better. Hoyt assured me that if I did so, and the drug was patentable, he would be pleased to pay me royalties. He offered me the position of Director of Research, which I promptly accepted and joined Carter Products in June 1949. I was happy at that time. My salary was \$12,000, which was more than double my university stipend. I could pay off my debts and my wife was pregnant and expecting in September. We rented an apartment in Metuchen, New Jersey which was convenient to the laboratories and plant located in North New Brunswick.

The laboratory facilities available at the time of my arrival were limited and consisted of facilities needed for the creation of new cosmetics, a control laboratory and a new, just initiated laboratory of

synthetic organic chemistry. The latter was headed by Dr. B.J. Ludwig, an excellent and imaginative organic chemist who became a friend and collaborator. There was no pharmacological laboratory and no animal house, and my first assignment was to have the empty space that was made available to me transformed in a manner to permit me to continue my research.

Dr. Ludwig suggested that the 2,2-substituted 1,3 propane diols should be evaluated for myanesin-like activity and we soon found that some of them had remarkable anti-convulsant properties. They also produced muscle relaxation and paralysis in large doses but in my opinion were not suitable to be developed as muscle relaxants because they produced excitation prior to paralysis. They were in this respect similar to the barbiturates. The compounds were also a poor strychnine antagonist, a property which I considered to be an important indicator of muscle relaxant and tranquilizing activity.

I was settling down at Carter Products, busy hiring pharmacologists, equipping the laboratories and making myself

generally useful. I started thinking of developing products that might fit the interests of Carter Products. I invented and patented a novel nitrogen free hypo-allergenic antipruritic, had it clinically evaluated, but was not persuasive enough to interest Mr. Hoyt in the marketing of it. An alginic acid containing product that, in my opinion, would have been superior to the Carter Little Liver Pills also proved unacceptable to management. I did not mind these disappointments as my main interest still was the development of a compound that would have the properties of Myanesin but would have a stronger intrinsic activity (i.e., more muscle relaxant activity per unit weight) and be longer acting. I kept busy trying to settle down in a new environment.

Through Chet Mowery who worked for Carter Products on the sales side, I met Jack F. McCarthy, Jr., who worked as an attorney in his father's office in Princeton, New Jersey. He and his wife and family became lifelong friends of my family and me. They helped to establish us in the area and persuaded us to settle down in Princeton where Jack lent me money for a down payment on a lot and helped me

to build my first home. Without his and his family's support life would not have been the same. I consider myself a truly fortunate man for having had - and having - friends like Jack and Cathy. We keep in touch to this day.

I was still anxious to find a muscle relaxant that would have a longer duration of action than Myanesin. Dr. Ludwig, with whom I discussed these ideas, felt that the idea of blocking the oxidation of the terminal hydroxyl group should be further pursued. We knew that succinic acid did this to some extent and suggested the evaluation of other organic acids such as carbamic acid. These compounds, i.e., the carbamate esters of the 1,2-propane diols produced paralysis of longer duration than Myanesin. When, in turn, the carbamate of 1,3-propane diols were prepared, compounds with longer duration of action were found. At that time, in 1949 and 1950, the duration of action was evaluated by determining the time for which a given dose of the drug protected a mouse from electroshock seizures. Electroshock was used because it was the only technique that could be used in the laboratory

with the equipment available at that time. The paper submitted for publication in 1951 appeared in the Journal of Pharmacology and Experimental Therapeutics in February 1952 and was the first paper mentioning meprobamate. The drug was promptly tried in the treatment of epilepsy by Dr. Stamps and Dr. Gibbs at the Neuropsychiatric Institute of the University of Illinois. It was proved ineffective in major epileptic seizures. This finding did not discourage me and I concluded my publication with the following sentence: "A fuller pharmacological study of these or related compounds may uncover compounds with interesting central depressant properties." This is exactly what I proceeded to do and published the results in 1954.

#### Myanesin as an Antianxiety Tranquilizer

In my clinical study "Oral Myanesin in the Treatment of Spastic and Hyperkinetic Disorders", which appeared in June 1948 there is no mention of the antianxiety effect of the drug. I was, however, very much aware of the existence of such an action for various reasons. To

begin with, I was impressed with the Myanesin-induced changes in behavior of guinea pigs. These animals, as is well known, are quite "nervous". They try to run away with great speed as soon as an attempt is made to pick them up. When given a small dose of Myanesin, they become quite friendly and do not object to being picked up and fondled. It is because of this observation that I described the action of mephenesin as "tranquilizing" in the first publication on this subject in 1946. In my clinical work in Rochester I became particularly interested in patients with tremors and involuntary movements. I noted that the tremors were greatly influenced by the emotional status of the patient. When a patient was made comfortable the tremors disappeared; when they felt tense and anxious the tremors increased in intensity. The tremors in these patients reminded me of those induced in anesthetized cats by injecting strychnine. They were relieved in both by mephenesin, which I knew by then to be an interneuron blocking agent. I used this name to describe the ability of a drug to block the spread of impulses in the inter-neuronal circuits. I



knew that the cardinal symptoms of anxious patients is overreaction to normal stimuli and concluded that the physical basis of anxiety was an increased responsiveness of the interneuronal circuits. Meprobamate was able to counteract the hypersensitivity of the interneurons in doses that did not produce any other pharmacological effects. I concluded that this was the physical property responsible for the antianxiety action of meprobamate and started using the interneuronal blocking action as the criterion in the search for more powerful and longer acting meprobamate-like agents. The papers describing the two best compounds I found - glyketal and meprobamate - had been published and I felt that it was time to discontinue the search for even better products and to concentrate on the development and clinical testing of the most promising one. Meprobamate was selected because it appeared less toxic. Unlike glyketal, it was also first prepared in Wallace Laboratories.

### Meprobamate

Dr. B.J. Ludwig synthesized meprobamate in 1950 and he and I

filed a patent application on July 29, 1950 (Serial Number 176.764) which described the preparation and central depressant properties of meprobamate and other dicarbamates of substituted propane diols. This application was refiled on August 3, 1953 as a continuation-in-part and patented November 22, 1955 (Patent No. 2,724.740.).

Before the end of 1951 enough toxicological animal data have been accumulated to start careful toxicity studies in humans. At that time we were in the habit of giving code names to compounds showing some promise. We used names of villages of the area around North Brunswick where the Carter Products plant and laboratories were situated. We had compounds names "Princeton" and "Hopewell" and happened to assign the name "Miltown" to the compound whose generic name now is meprobamate. To carry out chronic toxicity tests in animals we needed larger amounts of Miltown than our chemical laboratory was able to prepare. We found the large chemical firms such as Union Carbide or Dupont did not have enough faith in Carter Products to bother with the preparation of a few

hundred pounds of an unproven experimental compound. We were fortunate to have Bob Milano, the owner of Berkeley Chemicals, prepare it for us. We became friends and I was happy to see Bob being richly rewarded when he became the primary supplier of meprobamate powder when many tons per week of it were required.

Clinical trials with Miltown were begun in four different patient populations: psychoneurotics, true psychotics, epileptics and in patients with muscle spasms. It soon became clear that the classic symptoms of psychoneurosis such as anxiety, tension, insomnia and general hyperresponsiveness were well controlled by Miltown in the majority of patients and that the main indication for which this drug should be prescribed should be anxiety and tension states. Mr. Hoyt, the President of Carter Products, was not impressed with my recommendation to spend substantial amounts of money on clinical trials in this field.. To find out, he retained the Gallup Poll Organization to interview 100 medical doctors. Much to my surprise, the majority of doctors did not feel the need for an antianxiety agent

and were not sure whether they would prescribe such a drug.

At that time in the early 1950's I found it difficult to make doctors and clinical investigators enthusiastic about antianxiety drugs. Most psychiatrists went through psychoanalysis which made them think that anxiety and tension were good for the patients and tended to motivate them. Doctors were not aware and not particularly interested in Cattell's work which showed that anxiety is a single, well defined reaction pattern which is dysfunctional and as such the opposite of a motivational force. In addition, they were not concerned and not much interested in the biological basis of anxiety.

I had to think of ways to interest people in Miltown without bringing up basic scientific or philosophical aspects. I succeeded in doing that by making a movie. The motion picture showed the behavioral changes produced in rhesus monkeys by Miltown and compared them with those induced by barbiturates, chlorpromazine and reserpine. The movie impressively illustrated the effect of Miltown. After its showing at the meeting of the Federation of

Societies of American Societies for Experimental Biology held in San Francisco in April 1955 I was approached by people from the Wyeth Laboratories. They were interested in the product and wondered whether they could obtain a license. I put them in touch with Mr. Hoyt who was delighted to see their interest. After Wyeth had the opportunity to study all the pharmacological, toxicological and clinical data that I had accumulated, they were licensed to sell Miltown under their own trade name, "Equanil". By midyear the Food and Drug Administration found meprobamate, the generic term given to Miltown, safe and effective and both firms started selling the drug without delay. I jumped at the opportunity to learn something in the field of sales and advertising. I had no previous experience in these fields of endeavor and felt deep down that reputable intellectuals (which I thought I had been) would have nothing to do with that. Nevertheless, I enjoyed my contacts with the Ted Bates agency which was retained by Mr. Hoyt to do the advertising for Miltown. I soon found out that Ted Bates did not know too much about the promotion

of prescription drugs. All their previous experience was devoted to the promotion of over-the-counter products such as Carter's Little Liver Pills. To feel more comfortable working with Bates, I put down a number of ground rules that should be followed in the promotion of Miltown. These briefly were as follows: The purpose of advertising is primarily to tell the doctor what Miltown does and how it should be used. This would be done by direct mailings to physicians and by advertising in medical journals. We would not employ any detail men to visit individual physicians. All advertising would be factual and educational.

This method of promotion succeeded quite well and the annual sales in 1956 exceeded 50 million dollars. The sales of Equanil exceeded those of Miltown and the Carter Products Company greatly benefited by this because Wyeth, in addition to paying royalties, had to purchase meprobamate powder needed for the production of Equanil from Carter at a higher-than-cost basis. As a result of this success, Wallace Laboratories, a subsidiary of Carter Products, Inc.

had sales and earnings many times greater than the parent company. Consequently, Mr. Hoyt decided to rename the company Carter-Wallace, Inc. and to have it listed under the new name on the New York Stock Exchange. He made sure, however, to retain absolute control of the company by holding on to more than 50% of the shares.

I was annoyed that I did not receive any company stock and that I was not made an officer of the company. I also found my royalty agreement unacceptable and started pressing to have it changed. I succeeded only partially in this endeavor.

It became clear to me that even in America it is most difficult to change from the status of an employee to the status of a part owner of a company. I can now understand why young scientists that have breakthrough ideas that cannot be properly explored at a university are starting their own companies instead of joining established firms that are in a position to offer them all the facilities needed for research and would relieve them from financial and administrative worries.

Around 1964 Hoyt decided to reorganize the firm. Things were

going very well at the time. Sales of Miltown and Equanil exceeded \$100 million a year and more than one third of this amount was clear profit to the company. The additional products I introduced were, with one exception, successful and profitable. These were the muscle relaxant and analgesic carisoprodol sold under the trade name "Soma" by Wallace and "Rela" by Schering, the antidepressant Deprol, the antihypertensive Capla and the non-sedating tranquilizer Solacen (tybamate). Hoyt, at that time, was seventy and felt that he should start thinking about gradually handing over the running of the company to his two sons. At that time I was in complete charge of Wallace Laboratories which included sales, promotion, manufacturing and advertising, as well as research and medical services. The company, according to Senator Kefauver, who expressed his views during Senate hearings, was the most profitable pharmaceutical company in the country. I knew that this was true and felt responsible for it.

I attributed the success of Wallace Laboratories to the



promotion of unique and original pharmaceuticals that were more than slight modifications of existing products. The success perhaps was also due to the way the products were sold and promoted. I strongly believed, and still do, that detail men should not be used. Doctors should learn about new drugs from medical journals that publish peer-reviewed articles of controlled clinical trials. They should learn about them at medical meetings sponsored by medical or scientific societies that have no vested interest in the drug that is being discussed. Detail men are salesmen with little or no background in science and medicine that are trained by pharmaceutical companies to persuade doctors to prescribe their proprietary drugs. They should not be the main source through which doctors learn about advances in medicine.

In 1964 Hoyt retained an outside consulting firm to reorganize the company. At that time the annual sales of Wallace Laboratories, which was the division responsible for the pharmaceutical part of the business, greatly exceeded the sales and profits contributed by the parent firm selling proprietary medicines and cosmetics.

Nevertheless, Mr. Hoyt pointed out to me at that time that I had no business experience prior to joining him and that he felt insecure with a scientist like me who probably did not know how to read a profit and loss statement. During the following months I was gradually divested of all responsibilities other than pure research. I opposed all these changes as vigorously as I could. I pointed out how successful the firm had become under my management but all my protests were of no avail. Hoyt pointed out that I had a tendency to run a business as if it were a charitable organization. He was partly right in stating this because I do not believe that profits should be the sole motivation of a business. All I could do at that time was to accept the situation as gracefully as I could. I did not want to start looking for a new position at this stage of my life - I was over fifty. I had a group of devoted scientists in my laboratory and I was anxious to continue working with them on my favorite project which was a product that increased resistance to infections and cancer. I was convinced that such a product existed and was continuously being

produced in the body. I called this substance Protodyne.

### Protodyne

Since it has been discovered that infectious diseases are caused by microbes, it has been recognized that not all persons exposed to a disease-causing microbe will become sick. When Koch, at a meeting of the German Society for Pathology, demonstrated a culture of the cholera vibrio and remarked that the culture in his hand contained enough microorganisms to infect 10,000 humans, Professor Virchow, the President of the Society, took the culture and promptly drank it without suffering any untoward effects. Various explanations have been offered to explain this episode, but it did not change Koch's discovery that infectious diseases are caused by pathogenic microorganisms and that the only safe way of preventing or curing these infections is the generation and administration of specific antibodies in the form of vaccines or specific antisera. However, it is well known that not all people exposed to a pathogenic microorganism become sick. This natural resistance to infections has been known to

exist since the work of Metchnikoff at the Pasteur Institute in the late 1890's. After an extensive review of the world literature, I concluded that the substance responsible for the natural resistance to infections is endotoxin. Endotoxins are substances present in the cell walls of gram negative bacteria. They are abundantly present in the cell walls of *B.coli* which lives in the fecal material present in the colon.

Endotoxin isolated from the feces has been shown to increase the resistance of the host to many bacterial, viral and protozoal infections.

(Berger, *Advances in Pharmacology* 5: 19-46, 1967.) Moreover, endotoxin has been shown to produce hemorrhagic necrosis of tumors. Endotoxins, however, are not suitable for clinical use because of their toxicity. Doses that produce an increase of natural resistance also may produce high fever, leucopenia, profound vasomotor disturbances, shock and death. Many attempts were made to detoxify endotoxins by purification or chemical modification, but all these were unsuccessful.

A true breakthrough in my understanding took place when I discovered, together with my friend and associate. G.M. Fukui, that

the ability of endotoxin to increase resistance to infections is maintained or increased after repeated administration of endotoxin. This was in dramatic contrast with the development of tolerance to the toxic effects of endotoxin. After repeated administration of endotoxin tolerance to its toxic effects developed. At the same time tolerance to increased resistance to infections did not develop so that the same dose that was given at first remained effective on repeated administration. This indicated to me that the substance we call endotoxin must be a mixture of two substances; one producing effects against which tolerance can be produced and the other causing an increase of resistance to infections to which tolerance does not develop. It was clear to me that the availability of such a substance would be of great practical importance. At the present time protection for infectious diseases is produced by vaccination or immunization. These procedures achieve protection by the administration of attenuated or killed pathogenic microorganisms. By doing this the subject's immune system is induced to produce antibodies specific to

the pathogenic microorganism contained in the vaccine. On any subsequent contact with the pathogen these specific antibodies will combine with it and render it harmless. This process is highly specific. The measles vaccine protects only against measles and diphtheria immunization protects only against diphtheria. At present each child is vaccinated against at least six different diseases before starting school: diphtheria, tetanus, scarlet fever, whooping cough, measles, chicken pox and polio. As new pathogenic viruses are being recognized, new vaccines become available. Obviously it would be much simpler if the natural resistance to infections and cancer could be modified in such a manner so that we all resemble those of us that rarely catch infections or cancer. We are all aware of people who repeatedly are exposed to infectious agents or carcinogens, yet remain healthy. Examples of these are people who remain free of symptoms during influenza epidemics when exposure to the virus is unavoidable; people repeatedly exposed to the HIV virus who remain healthy; and inveterate smokers free from lung cancer after smoking two to three

packs of cigarettes a day for more than 30 years. To explain these variations of susceptibility to infections and cancer I assumed that the process is controlled by the way we handle the bacterial flora in our guts. E.coli is always present in the colon in abundant amounts. This microorganism is an excellent source of endotoxin which is also present in the gut. I decided that the way to proceed was to try to isolate from E.coli the resistant increasing part of endotoxin to which tolerance on repeated administration does not form.

In the late 1960's there was a great interest in endotoxin. Many scientists worldwide attempted to isolate endotoxin in its purest form so that its chemical structure could be identified and eventually synthesized. The test used to follow purification was the pyrogenicity, the fever inducing property of the isolated compound. I thought that this was not an appropriate test because pyrogenicity was an undesirable property of endotoxin. The action of endotoxin that was of interest to me was its ability to increase general susceptibility to infections. I became more and more convinced that the property was

unrelated and different from pure endotoxin. I became sure of that when I found that tolerance to the protective effect did not develop. I also noticed that different chemical methods of extraction of E.coli yielded products of similar pyrogenicity that however greatly differed in their ability to increase resistance to infections. I decided that the proteinaceous material that is usually thrown away during the purification of endotoxin should be examined. This proteinaceous material which is contained in the hot phenol used during the purification contained the desirable fraction which increased resistance to infections and was not pyrogenic. It was further purified and named Protodyne.

I felt and still feel that this substance plays an important role in the ability of individuals to fight infections. It does this without delay as it is effective immediately after administration. Its protective action is different from that of vaccines that depend on the formation of specific antibodies that take several days to develop. Protodyne increases resistance to all microorganisms and viruses for which it has



been tested, including the Rous sarcoma virus. It has another property that indicates it is of biological importance. Its ability to increase resistance to infections is not inactivated by plasma. This is in contrast to the inactivation of all biological effects of endotoxin by plasma.

After considering all I knew about protodyne, I wanted to actively pursue research in this field. I felt and still do that protodyne or a similar substance plays an important part in defining the marked differences in susceptibility of people to infections and cancer. I wanted to devote all my energies to this subject. I have not been very successful. My influence at Carter Wallace was changing. This was in 1968. I was no longer listened to; my influence, my power and the funds made available to me were diminishing. I was made to feel that I was no longer wanted or needed. I was informed that in the future it would no longer be up to me what Wallace Labs would sell. It was suggested I retire to receive an annual salary of \$100,000 on condition I sign an agreement not to work in the pharmaceutical industry for the

rest of my life. I was in my late 50's and in no mood to retire. I wanted to develop protodyne as a product that would increase the natural resistance to infections and cancer, and was looking for a place where this would be possible. I have not found such a place.

I still believe that the marked individual differences in susceptibility to infections and cancer are best explained by the presence of protodyne, or a similar substance of that type, in the intestinal canal. E. Coli and other microorganisms containing protodyne are present in the gastrointestinal canal in very large numbers. As they disintegrate they are releasing protodyne, which is absorbed into the blood. Protodyne, like endotoxin, has a non-specific and rapid antimicrobial action that is independent of the presence of specific antibodies. It differs from endotoxin in retaining its effectiveness in the presence of blood and in not being inactivated by serum of plasma. These conclusions are well supported by my and George Fukui's publication. I regret that we have not been given the opportunity to continue working on this project but feel confident that

these ideas, in due course, will be picked up, verified and used.

### Immunoadjuvants

Through my good friend, Louis Chedid, who was Director of Research at the Pasteur Institute in Paris, I became interested in immunoadjuvants. These are substances that increase the formation of antibodies to specific antigens. There is need for such substances because many pathogenic microorganisms do not induce strong formation of specific antibodies. The available stimulants such as Freund's adjuvant are too toxic for clinical use. I collaborated with Dr. Chedid's group and played some small part in the development of several adjuvants that appeared to have great promise in laboratory animals. For some reason, Chedid was never able to engender enough interest in any of the firms that manufacture vaccines. I cannot understand why these products that looked so impressive in laboratory animals have not been accepted for use in humans. I must try to find out.

## Chlorphenesin

Chlorphenesin is chemically closely related to mephenesin from which it differs in having a chlorine group in place of the methyl group on the phenol ring. It possesses similar muscle relaxant properties as mephenesin and was first described as a muscle relaxant substance in the original mephenesin paper in 1946. I have always been interested in the broad concept of interference with immunological reactions by simple chemical compounds and in due course decided to study the effects of propane diols along these lines. My interest in this field had been revived in 1961 when Kessel and Broughton, graduate students of my friend Werner Braun have shown that peritoneal phagocytes from guinea pigs tested with meprobamate behaved like cells obtained from immunized animals in not supporting intracellular growth of *Brucella abortus*. To see whether this compound would also affect other immune responses, the effect of meprobamate on the passive cutaneous anaphylaxis reaction elicited in

guinea pigs with penicillin conjugates was investigated. Meprobamate did not interfere with this reaction, but certain phenoxy propane diols did. Of these Chlorphenesin appeared to be the most effective. The effect of this substance on the immune response was studied and was found to have some unusual properties. When chlorphenesin was administered together with an antigen, the formation of humoral antibodies was suppressed. Chlorphenesin given by itself before or after or simultaneously, but at a different site, did not affect antibody formation. This observation, when first published, did not have any practical application. It may have some utility now. Since 1969, monoclonal antibodies have been discovered and came into wide clinical use in a variety of clinical conditions. Formation of antibodies to the monoclonals is sure to occur and it is possible that these antibodies interfere with the action and effectiveness of the monoclonals. The administration of chlorphenesin simultaneously with the monoclonals would prevent the formation of the anti-antibodies and thus may increase the clinical effectiveness of the

monoclonals. I regret to say that up to the present, I have not managed to get anybody interested in this possibility.

### Atherosclerosis

Ludwig and his associates in a program originally aimed at obtaining better antianxiety and anticonvulsant products, prepared a series of hydroxylamine derivatives with promising hypocholesteremic activity. Some of these compounds were of interest, not only because they reduced serum cholesterol concentration, but mainly because of their ability to reverse experimentally produced atherosclerotic lesions. The best compounds of this series were called W-398 and W-1372. We have never succeeded in elucidating the mechanism by which these drugs lowered serum cholesterol and caused retardation of atherosclerotic plaque formation. In view of this I thought it best not to initiate clinical trials with these substances. This decision, no doubt, was also influenced by the turmoil resulting from the organizational changes taking place at that time. I have, however, seen to it that all experimental data that we

have developed would be published.

### My Retirement

In 1972, two unexpected events suddenly occurred that changed the course of my life. On November 6th, 1972, my wife suddenly died in her sleep of cardiac arrest. This event occurred when I, with my older son Franklin was in London. We were having dinner at the apartment of my friend, Sir Charles Dodds when the news arrived. We returned home immediately. Bozena's death deeply affected me. I did not wish to live in Princeton any longer. I was now alone in the lovely and spacious home that Bozena built and in which my two sons grew up. Bozena was gone and the boys were in college. All my friends in Princeton were married and it did not feel right to me to be with them without Bozena. In addition, two of my closest friends also died quite unexpectedly during the fall of 1972. One was Dr. Arthur Tobolsky, a professor of physical chemistry at Princeton, who died suddenly of a cerebral hemorrhage in October at the age of 48. The other was Werner Braun, professor of microbiology and bacterial

genetics at the Waksman Institute of Microbiology of Rutgers University. He died in December of a massive heart attack.

The death of Werner Braun affected me deeply. He was a close personal friend who had an understanding of the problems I had with Carter Wallace. He had interest in my protodyne project and was of great help to me in introducing me to the key people in the field of endotoxin and non-specific immunity. This was very helpful to me because, since 1944 when mephenesin appeared on the scene, I lost all my contacts in the field of microbiology and immunology.

By the end of 1972 I felt so uncomfortable at Carter Wallace that I decided to move on. I rented an apartment in New York City and started to look around for opportunities. During the past 15 years I had numerous job offers which I invariably rejected without further investigation. Now I became receptive to these offers, but found that after a first enthusiastic interview there was no follow-up by the prospective employers. I confronted Mr. Hoyt with the problem. Hoyt told me that Mr. Peake, at that time the President of Carter



Wallace, found out that I wanted to sell the Wallace Laboratories Division to Hercules. This was utter nonsense! I did not own Wallace Laboratories, so how could I sell it. In addition, I did not know anybody at Hercules and never had been in contact with them. My telling Hoyt all this did not seem to make any difference. He refused to discuss this matter with me further and made himself unavailable to me. My situation with Carter Wallace became very difficult. I was ignored by management, who hired new heads of departments that previously reported to me without discussing the matter with me. There was nothing left to do but to resign, which I did in April 1973. There was no gold watch or golden parachute - and no separation pay.

After I moved to New York in 1973, I met a delightful woman, Christine Anderson. I soon became deeply impressed with her cheerful disposition, her charm, and her wisdom. We spent a lot of time together and promptly fell in love. She made me understand that being President of Wallace Laboratories need not to be the most important thing in the world. We traveled to exotic places such as

Bhutan, Kashmir and Afghanistan, and in May, 1975, got married. Her interest in the arts, sports - she is an outstanding tennis player - and her enjoyment of social and cultural activities greatly enriched my life. She has been, and is a wonderful companion by being both caring and understanding. I am fortunate to have her as my wife.

Although I retired from Carter Wallace, I did not plan to spend the rest of my life playing golf. I never learned to play the game and I did not want to learn, as I had more interesting projects on my mind.

One of the projects that came my way at that time was at the American Institute for Economic Research in Great Barrington, Massachusetts, where there were problems. The Institute was founded and run by my old friend, Colonel Harwood, and its aim was to establish a scientific basis for research in economics. The funds needed to sustain these research programs were obtained by providing investment advice to individuals and by operating charitable gift annuities. In these programs, prosperous individuals made a tax-deductible gift of appreciated stock or cash to the Institute. The funds

were invested and used to pay a lifetime annuity to the donor. At the death of the donor, the remainder of the gift that had not yet been distributed as an annuity became the property of the Institute. The Internal Revenue Service objected to the Institute's practice of investing substantial amounts of money into South African gold mines because of apartheid. The Institute wanted to invest in South African gold stock because of the high dividends they paid. At that time, I was a Trustee of the Institute and recommended that the matter be discussed with the IRS and a compromise sought. This attitude was vigorously opposed by my good friend and fellow trustee, John Exter, who felt that the government had no right to interfere with investment decisions of private individuals. I felt that I should do what I could to preserve the continuing payments of annuities and continued existence of the Institute by discussing the matter with the government, thus avoiding costly legal proceedings and political action. Most of the Trustees agreed with me and I was elected Executive Trustee. The matter was eventually settled in the best possible way for all

concerned parties. Most of the South African gold stocks were sold before gold lost most of its value and the annuitants and Institute continued to benefit from alternate investments. I owe a debt of gratitude to Col. Harwood who taught me all I know about investing during the 30 years we were friends. As a result of this I have made many times more money by investing than I ever made from all my inventions and patents. Col. Harwood's philosophy, his writings, and the Institute are still available, and I recommend them highly.

Felbamate - *or what your friends can do to you*

Felbamate is the generic name of an anticonvulsant put on the market by Carter Wallace, Inc. in 1994. I am devoting more space to it not only because I have been involved with this compound for more than 50 years, but because I want to generate interest in its actions so that these would be further explored.

When I first joined Wallace Laboratories in 1949, there were no laboratory facilities available. I had to build these up from scratch. I was aware that mephesisin had some anticonvulsant action and as I

wanted to find an improved mephenesin the evaluation of the anticonvulsant activity of its congeners appeared appropriate. Testing for anticonvulsant activity is relatively simple; the machines to administer electroshock are readily available; and the tests can be carried out on mice. Dr. Ludwig prepared a number of derivatives of 1,3-propanediols. We found that the 2,2-diphenyl 1,3 propanediol monocarbamate possessed a powerful anticonvulsant activity of unexpectedly long duration. We applied for a patent which was issued on October 20, 1953 (US Patent # 2,656,378). I was anxious to have this compound evaluated in humans as a drug for the treatment of epilepsy. After discussing this at some length with Mr. Hoyt it was decided that in view of the high cost of the chronic toxicity studies that were mandatory before the compound could be evaluated in humans and the relatively small number of people suffering from epilepsy it would be prudent to preserve the available funds until a product with a larger market potential became available. I believed at that time, in 1952, that meprobamate would be such a compound. After

meprobamate became a success in 1955 and funds became available that could be used in evaluating products that would be of value in the treatment of diseases less common than anxiety, we evaluated all compounds made in connection with the meprobamate project for anticonvulsant activity and found that 2-phenyl-1,3 propanediol dicarbamate (also called Phenamate or W554) was the most active. A patent was applied for and issued on April 26, 1959 (Patent 2,884,444). After chronic toxicity studies were successfully carried out, clinical trials in epileptics were started in the early 1960's. The drug appeared to diminish the incidence and severity of epileptic seizures but the investigation was discontinued as management felt that the market for antiepileptic drugs was too small to justify a substantial investment needed to accurately assess the clinical value of the drug.

I was greatly surprised when I read in the Value Line Investment Survey dated October 18, 1991 that Carter Wallace had filed a new drug application for Felbamate. I noted that as a result of

this, the Carter Wallace stock rose from about \$53 to about \$131 resulting in an increase in the market value of Carter Wallace stock of about \$1.2 billion. I also noted that Schering-Plough, an important multinational pharmaceutical firm, paid Carter Wallace \$10 million as an advance payment for the license to sell Felbamate outside of North America (Wall Street Journal, April 7, 1992, page C-2, column 4).

As I was reading about all these riches, I remembered that back in 1949 I accepted my position with Carter Products (now Carter Wallace, Inc.) on condition that I would receive part of the proceeds of sales of products I invented. There was no question in my mind that I invented Felbamate. I got in touch with the management of Carter Wallace and drew their attention to these facts.

Subsequently I learned from the literature about all the work that was done by Carter Wallace since the middle 1980's. I was hurt by not being told of this, particularly because I considered Charles O. Hoyt, who was Chairman of the Executive Committee and in charge of pharmaceuticals of Carter Wallace, as my friend. He had many

opportunities to tell me about it as we met socially several times each year in New York or at his second home in Paris.

As time went on I learned more and more about all the work done with Felbamate. An article published in the "Editorial and Commentary" section of the Lancet of June 5, 1993 entitled "Felbamate: a new antiepileptic drug" by Martin J. Brodie was particularly helpful. The article stated that the drug was synthesized in 1955, but that clinical development began only in 1982. This was incorrect as I had initiated clinical trials of the drug in the early 1960's.

A patent search revealed that after my departure, Carter Wallace actually applied for two patents, one on the synthesis (US Patent 4,868.327 issued September 19, 1989) and another on the anti-epileptic action (US Patent 4,978.680 issued December 18, 1990). One wonders how it is possible to patent an invention that has been previously patented. This, of course, is not done and would not stand up in court, but to litigate can be very costly and is not a viable way for an individual with limited means. But soon all this was of little



importance. In August 1994 the Food and Drug Administration made it known that administration of Felbamate was linked to 10 cases of aplastic anemia and recommended discontinuation of the use of Felbamate. As a result of this Carter Wallace shares plunged, losing nearly a third of their value. Subsequently, the firm discontinued all pharmaceutical research. I was sorry to see the disappearance of the laboratories that I carefully built over many years, but I had to let it be. In this world nothing is forever.

Nevertheless there are important lessons to be drawn from the Felbamate story. Millions of people have been taking closely related propanediol dicarbamate compounds for over 30 or 40 years without a single case of aplastic anemia or other blood dyscrasias ever having been reported to be caused by these compounds. Yet Felbamate was taken by relatively few people and it appeared to cause dyscrasias in about one out of 5,000 people. Is there an animal species sensitive to the toxic effects of Felbamate? Studies of this kind would be of value in evaluating toxicity of new drugs in animals prior to the

commencement of clinical trials in humans. Another question worth close study would be to find out what other drugs were taken by the people intolerant to Felbamate.

It should not be forgotten that Felbamate has another action that is perhaps more important than its anti-convulsant activity. I am talking about Felbamate's ability to prevent and perhaps counteract cerebral ischemia and hypoxia. It may be that some closely related compounds that have proven to be non-toxic, such as meprobamate, carisoprodol, tybamate or butamate have a similar ability to reduce hypoxic-ischemic brain damage. I wish it were in my power to initiate or carry out such a study as non-toxic compounds with such an action might be of value in the treatment and prevention of heart attacks and strokes.

### Silvio Garattini

I do not want to conclude my story without paying homage to my dear friend Silvio. We met in the late 1950's at a meeting held at the University of Milano where Dr. Garattini was Professor of Pharmacology. There was a lot of interest in meprobamate at that time and I found Garattini an unprejudiced and independent thinker with understanding of, and insights into, biological psychiatry and psychoneuropharmacology. We met from time to time at scientific meetings and congresses, and I was greatly impressed not only with his brilliance and versatility as a scientist but also with his ideas and attitudes as a human being. He believes, as I do, that one of the basic human rights is the right to receive the best medical care irrespective of one's wealth or station in life.

He adopted three severely handicapped babies from the Milano orphanage. He brought them up together with his two biological sons to become well-adjusted and self-supporting individuals. He did this

because he knew that a person in his position had better access to the best medical care than most other people. His advice and help was always freely given to all who came to ask for it. I knew that Silvio served as a consultant to Mario Negri, a prosperous Italian industrialist who owned a chain of jewelry stores. Mario Negri wanted to get into the pharmaceutical business and Silvio helped him to establish contact with Borough-Welcome in England. I once met Mario Negri at dinner and was impressed with his personality. Nevertheless, I was surprised when I learned in 1960 that he died and left in his will a substantial amount of money to be used for the establishment of a non-profit medical research institute. Dr. Garattini, in Mario Negri's will, was named Director of this institution. Thanks to Silvio's enthusiasm and ability to solve and overcome legal tangles, the building of the facility was promptly started and the Institute was opened for scientific activities in February, 1963. It has been thriving and growing ever since and is well known by scientists worldwide for its contributions to the understanding and treatment of cancer, cardiovascular and

kidney diseases and mental and nervous diseases.

The ideas and principles that made the Mario Negri Institute so successful were formulated by Silvio Garattini. As I see them, they are as follows: Research should be carried out for its own sake. Only if we understand the causes of disease can we intelligently work on its prevention and cure. Scientific research has to be completely independent and free from establishments that have a vested interest in the undertaking. These include industry, the universities and the State. This independence is important in order to free the researchers from prejudice, bureaucratic restrictions and political pressure. This philosophy has been described as “private efficiency serving the public interest.” It is the policy of the Institute not to patent any of the discoveries that have been made. The results of all investigations are freely published and made available to the public.

It is wonderful to behold that, in spite of these restrictions that would be expected to severely limit funding, the institution has been rapidly expanding, not only in influence and scientific contributions,

but also in the number of scientists and facilities and locations. From modest beginnings in 1963, the Institute now has expanded at its original location in Milan, opened additional laboratories and research facilities in Bergamo and S. Maria Imbaro. In addition, a clinical research center for rare diseases, called Villa Camozzi, has been opened in Ranica. The creation of this clinical center is particularly heartening because rare diseases are rarely subject to intensive study. Yet rare diseases affect many people: more than 1000 such diseases have been described. Also some diseases that at one time were considered rare occur quite frequently and are considered rare only because of our inability to diagnose them. An example of this are heart attacks that during my student days were considered a rare disease and are now recognized as one of the most common causes of death. This must have been suspected by William Harvey who wrote in 1647, "...there is no better way to advance the proper practice of medicine than to give our minds to the discovery of the usual law of nature, by careful investigation of cases of rarer forms of disease."

### What I Believe

By age twenty I had a pretty good understanding of what was going on in the world. I realized that this is not the best of all possible worlds and that most people, while not all bad, are in some respects prejudiced and evil, and not fully able to understand what is going on around them. I saw the pain and injustices suffered by many people around me and decided that there cannot be a loving and benevolent creator that demands frequent acknowledgments of his powers in the form of prayers. That does not mean to say that I failed to recognize spiritual values. I believed, and still do, that most people know what is right and what is wrong in any one particular situation but find it hard to formulate rules that would be generally applicable. I am impressed with the majesty of nature and the beauty of natural phenomena, but feel that these are not necessarily created by a supernatural power. I feel that we cannot at this time explain and understand how they arose. Nevertheless, I remain anxious to understand and feel that the only way to the understanding is not

through revelation or other non-verifiable supernatural ways, but only through accumulation of factual knowledge that can be reevaluated by independent, unprejudiced observers.

On a more terrestrial level I feel that all violent behavior is wrong. It should be avoided and prevented. This goes particularly for wars. No problem has ever been solved by waging a war. As a result of this, I became a conscientious objector. I never joined allied forces, not even when some of my best friends and some of my family were persecuted, put into concentration camps or killed by Hitler's cohorts.

When I came to the United States and my children were born I felt that I should have a religious affiliation. I joined the Unitarian Church in the early 1950's because it gave me the opportunity to express freely my beliefs. These are summarized in a sermon entitled, "Religion, Science and Unitarianism", which is reprinted in the Appendix. After having lived so long and having seen so much, I feel that the principles by which the Quakers try to live should be more widely adopted.