SECRETS OF AUTOIMMUNITY

From Experimental Research to
Treatment of Autoimmune Diseases

Peter Anton Miescher

80 YEARS OF A SERENE DREAMER
A PASSIONATE SCIENTIST
AND A CLINICAL IMMUNOLOGIST:

A LIFE-STORY

Dedicated to Family and Friends,
Urbino, July 2005

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PROLOGUE

During the 20*th* century, developments and progress in medicine were extraordinary and I had the privilege to participate actively in the field of clinical and experimental immunology. In the 1940s, ignorance about the cellular events in immunology was almost complete. I thus had the opportunity to work in "virgin" territory where almost everything was still to bediscovered.
When - in March 2005 - Annatina Miescher (81 years old) asked me to write about my long journey from childhood to old age (81 and a half), I hesitated at the prospect of describing a very confusing mix of private life and a complex research and clinical career. However, I finally felt the obligation to follow her initiative as throughout my career she has been my collaborator, providing encouragement and constructive criticism and, as of 1960, sacrificing her own career as an ophthalmologist. She has been, and still is, a constant source of inspiration and support in my personal and professional life. "Our story" might be of interest to our family and friends.

In this concise review of my career I mention the various circumstances that awakened my interest and motivated me to explore the field of clinical and experimental immunology.

1. Childhood (1923 - 1941)

In my early childhood I was, so I was told, a dreamer. After I started school, I gradually became an "explorer" trying to solve problems such as how a watch works, or studying the anatomy of a bug. At the same time, I entered the world of music: the first year with the piano, subsequently with the 'cello. At the age of nine, I was introduced into the sphere of chamber music (sonatas, trios and string quartets). To play with other musicians was an artistic event, but also gave me an example of teamwork. At 12, I joined the school orchestra. In 1941, I was soloist for the Boccherini cello concerto, accompanied by the school orchestra. Music aroused feelings of joy, love and sadness that I had never experienced before. I became eager to better understand the human soul and behavior, which brought me to the university library where I discovered the works of Freud and Adler, the former focusing on sexuality, the latter on the power-drive, expressions of life man shares with animals. The study of philosophy showed me the difference between animal and human behaviour. I started to read about the philosophy of Socrates in Plato's work, and continued with Aristotle. Socrates defended the conception of the human soul as the seat of both consciousness and moral awareness. The thinking of Socrates and Aristotle led me to the foundation of today's concept of democracy (insisting on the right and the capacity of the people to act either directly (Aristotle) or through representation (Socrates) to control the institution of the republic.
Professor Wehrli at the University of Zurich was of great help with my philosophical studies. He replaced our regular Latin master for a 6-month period. Instead of reading "De Bello Gallico", Wehrli introduced us to Severimus Boetius and his masterpiece "De consolatione philosophiae", written in prison. Boetius had been put into prison on false charges of treason and was finally executed without trial, which greatly offended my sense of justice.

Peter Anton Miescher born in Zurich 1923

…a fine observer

…an optimist since ever

studying a bug

1932 Peter Miescher playing cello.

PETER MIESCHER

Student at the Conservatorium in Zurich (class of Reitz). 1937-1941 active member Of the Zurich Gymnasium student orchestra. 1942 soloist for Boccherini concert.

…and 60 years later
(Dr. med. Walter Blumer, piano)

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During my teens, I discovered the pleasures of mountain climbing with my father, not so much for the challenge of outperforming others as for the contact with nature. When one is above 4,000 m, looking towards the far horizon, man appears very insignificant facing eternity and feeling the spirit of God. Once, traversing a very narrow and icy slope (from the Dom to the Taeschhorn) above an almost vertical 1,000 m wall, I missed my step on the ice and fell. Sliding rapidly, together with our guide, towards the precipice, I was sure that I was going to die. Astonishingly, my father managed to hold both the guide and me. Waking from this potentially fatal accident, I formed and kept a deep admiration for my father.

In 1939, my parents took me to study with the protestant pastor in Morrens sur Lausanne. In this pleasant environment, I started to learn French. The pastor also introduced me to the films of Marcel Pagnol (Marius, Fanny, César) which made me want very much to see the South of France. After a visit to my godfather in Geneva, I sent a postcard to the pastor and turned my bicycle southward instead of returning to Morrens. I enjoyed a wonderful journey down the Rhone valley on my bike. Once south of Orange I no longer slept in inns but preferred to sleep under olive trees on these mild summer nights. Those nights were another dream world, starting with the evening concerts of the famous crickets. When choosing a place to sleep amongst the olive trees, I used to look for an old one about 50 metres from the road. I would then put an iron chain around the tree, attach the bicycle to the chain and then attach one of my legs to the bike - all this to make sure that no-one stole my bike while I slept. I continued my journey and all was well until suddenly there seemed to be a lot of nervous activity. Soldiers were everywhere and then loudspeakers announced that war had been declared and that a general mobilization of the army had been decided. And so I had to return immediately to Switzerland. To make my journey easier, a French soldier let me hold on to his army vehicle. After Lyon, I realized that I had lost

all feeling in my right hand - the Condor is a heavy bicycle with low handlebars which meant that there was constant pressure on my palm, compressing the median nerve. This was when I learnt about how much time it takes to regenerate a damaged nerve: two weeks in my case.

Going back to my earlier school years, at that time my family went twice per year on a mountain holiday. In 1933 and 1934, we had our summer holiday in Ftan at the Hotel Bellavista (interestingly, four generations of the Miescher family are listed in the Ftan hotel registration book between 1880 and 1934!). But, more important for my life, my family became acquainted with the Lotscher family. My mother and my older brother frequently visited Mrs Lotscher, my future mother-in-law (during this period, my future father-in-law, a Swiss pioneer in the construction of galleries and tunnels, was working in India and Iran). I did not go with my mother, but she told me how much she admired Mrs Lotscher and her charming daughters. Instead of attending these tea parties, I followed my drive for independence. Several times (at the age of 10) I walked right down to Scuol (500 metres lower than Ftan) and, after crossing the bridge over the Inn, walked up to Vulpera (200 metres higher than Scuol), where I enjoyed swimming in a large pool. Still on foot, I returned to Ftan the same day, having walked more than 20 km.
One day, watching the herdsman with his goats, I felt the desire to accompany him up to the mountain slopes above the forest. My parents agreed and I spent several days walking up to the highest mountain meadows, above 2,500 m. It was a wonderful experience which I have never forgotten. In the morning, when the herdsman went through the village blowing his horn, I quickly dressed myself to be ready at 6 o'clock. The next 12 hours I spent in a dream world with my 60 goats, with ample time to think and to contemplate. At 18h00 we had to be back as the goats had to be milked.

At that time, Ftan was an idyllic village with proud people, enjoying an independent life. Many of the locals had worked in foreign countries when they were younger. They kept an open mind, knowledgeable about the culture of the country where they had worked decades ago. Some quoted Shakespeare, some Goethe, others Andersen, but most of them quoted Dante! Ftan was a most important point of reference in my life, long before marrying Annatina Lotscher. Understandably, we later built a family home there, enlarging a 16`h century country house, and acquired adjoining meadows which, with time, we turned into a garden-park. In the meantime, we have entrusted this home to our son and his family, who are deeply attached to the old place.

In Ftan

2. University (Medical school) 1942 - 1948 and first years with own family

After completing my secondary education at the gymnasium (Maturitat) in 1942, I decided - against my father's advice - to study medicine. I wanted to learn more about the human being with the final aim of fighting disease. In October 1942 I took the train to return to the canton I had enjoyed so many years before when I was in Morrens. Going through the Chexbres tunnel, I was again overwhelmed by the grandiose view of the vineyards, the huge Lac Leman and, at the far left, the Dents du Midi. The vineyards were still full of grapes, which contrasted against the beautiful autumn colours of the leaves. My life took a new turn right at that moment.

The Lausanne School of Medicine was renowned for the high quality of its professorial staff. George Nager, a friend from Zurich, reserved a large, comfortable room for me in the dormitory of a former boarding school. The building was located in a large park where I later used to prepare for my examinations. In addition to George, a number of other students also lived in this dormitory so I did not suffer from solitude. We often spent the evening together in one of the picturesque villages in the "Gros de Vaud".

One day, George and his friend Rolf Schild, president of the "Singing Students Association", invited me to an "initiation" meeting. To become a member of this association, one had to pass the "drinking test". Unfortunately for the president, whose drinking capacity I had to match in order to become a member, my alcohol tolerance surpassed his. However, I went home with a severe headache and decided not to join the Singing Students.

The lectures were most stimulating, particularly those by Professor Mathé who taught zoology, including animal behaviour, and by Professor Perrier, who gave fascinating demonstrations of electrical phenomena during the physics lectures.

My preparation for the first propedeutic examination brought me into contact with a charming fellow student, Claude Mieville, with whom I spent many days in discussion about the various topics, but also about philosophical questions. We were both followers of Platonic philosophy and were thus opponents of intolerance in general but specifically of the barbaric strategy of Adolf Hitler during those sad war times.

In the following years I continued my studies at the University of Zurich with excellent professors such as W. Hess (Nobel prize for physiology), H. Moser, a genius in microbiology, W. Loffler, an outstanding humanist and internist, G. Fanconi, the world's most famous pediatrician at that time, to name but a few. Immunology was taught by Professor Grumbach, an outspoken personality who brought so much confusion to this emerging discipline that I decided to get first-hand information at the University library. Although 50 years had passed since the discovery of antibodies by von Behring and Kitisato, I was struck by the many still open questions, including the possibility of autoimmunity, which had been raised by Metalnikof. Thus, the confusing lectures of Professor Grumbach were the initial trigger of my decision to actively participate in the investigation of the vast field of immunology.

In the clinical semesters, Loffler taught us the global approach to the patient and the importance of following a straight strategy of treatment. He also introduced us to the history of medicine, with special emphasis on Claude Bernard. Indeed, Claude Bernard too had lived at a time of wars, with an increased need for practical physicians. During the reigns of Napoleon I and Napoleon III, wars became extremely bloody, particularly at the battle of Solferino. With the increasing need for practical surgeons, the French government proposed separating the school of medicine from the university, considered to be an expensive luxury. Faced with this conflict of interest, Bernard wrote his famous book on the study of experimental medicine. In particular, he encouraged students not to take everything taught today as infallible but to remain critical since 50% of what is believed to be true today will turn out to be wrong tomorrow. “Il faut douter, fuire les idées fixes et toujours garder la libertè d'esprit “.

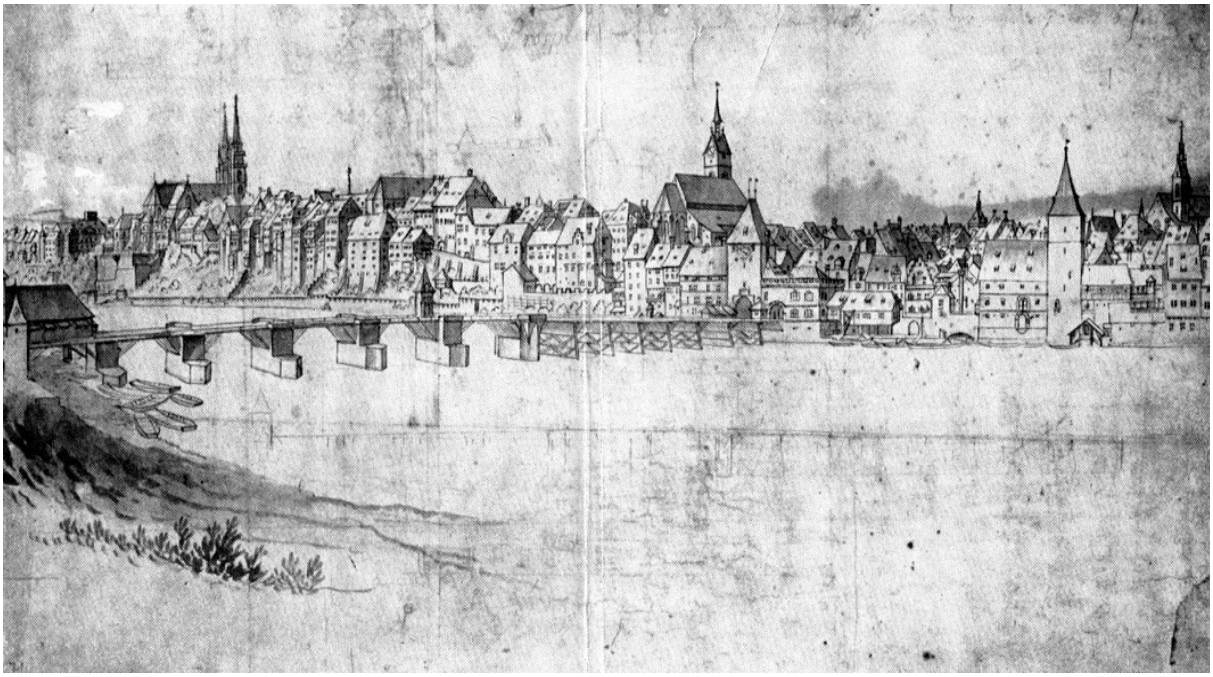
When the Second World War ended in 1945, we students wanted to travel beyond Swiss borders. In 1946 I went on a trip with Andreas Briner, a friend from the school orchestra. We took the train to Paris, where we stayed for three days. We were impressed by the beautiful city but most of all I was overwhelmed by the exhibition of modern art. In particular, I was fascinated by Matisse, Juan Gris, Lèger, Braque and Manet. Back in Zurich, I suggested to my father that he should acquire paintings by these artists rather than to continue collecting Old Dutch paintings. My efforts to convince him were unsuccessful.
My circle of friends grew during the clinical semesters. George Nager and his friend Mathilde Hofstetter were two years ahead of me but were part of the inner circle of friends. Walter Bessler was an especially close friend. We spent a summer vacation in St. Gallen in the department of pathology. George at that time was a clinical fellow. We learned a lot from the confrontation of clinical findings with anatomo-pathological data. Professor Uehlinger was a very sharp-thinking pathologist who frequently led our discussions. During this period, I contracted a severe form of varicella with central nervous system involvement for which I was hospitalized. Walter Bessler and George Nager visited me daily and helped me recover from this aggressive form of varicella. At this time, we decided to visit Italy together and immediately made hotel reservations in Florence, Rome, Naples and Ischia. It turned out to be one of the most outstanding post-war discoveries for us. We were fascinated by Italian architecture, the Italian way of life and the dream world of Ischia, not yet overrun by tourists. One special event was an excursion to Monte Epomeo. Industrial agriculture had not yet reached this region. Between vineyards and olive orchards, country people were working with donkeys, always singing with their sonorous voices. It was a really bucolic scene of times gone by. In the evenings, crickets in the hills competed with groups on opposite hillsides, their concerts filling the air in alternate waves.

During the clinical semesters, I also became involved with friends of the opposite sex. In particular, I was attracted by a student who fascinated me by her special temperament, approaching all subjects with an extraordinary freshness of mind and who, during lectures, would sketch colleagues and professors, capturing the essence of their characters with a few strokes of her pencil. The encounter with Annatina finally took place in the pediatrics auditorium. After exchanging a few words, we felt as if we were old friends. In fact, Annatina Lotscher had known my family since 1933 when my mother often visited Mrs Lotscher during our summer holidays in Ftan. We quickly realized that we had much in common as regards general interests while being very different in terms of temperament. I was fascinated by Annatina's extraordinary personality: full of energy, a pure soul, very intelligent, grasping a situation within seconds, and a universal knowledge and culture. I was deeply impressed by the uniqueness of her personal radiance: she has since then been the main source of joy to me.

A few years later, at our wedding, Uncle Max (my father's brother) immediately saw that Annatina would become the "motor" of the new family. He was right. Without Annatina's encouragement and help, I would not have been able to embark, as I had chosen to, on a most difficult career as a clinician and scientist, especially with a research topic considered at the time as most esoteric. Nobody could foresee 50 years ago that autoimmunity would become the most frequent cause of diseases affecting more than one in 10 people worldwide.

We had to manage on a minimal budget, since my father, in the old Basle tradition, insisted that we live on the very small stipend offered at that time to research fellows.

Before the wedding, we confronted another calvary. In 1946, Annatina, working with tuberculous patients sent to Switzerland by the Red Cross, contracted a severe tuberculous pleurisy. Fortunately, Professor Loffler was able to help me obtain the first anti-TB drugs: first a liver-toxic sulfone derivative, subsequently the first samples of streptomycin which were toxic for the inner ear, then the less toxic dehydrostreptomycin, and finally paraminosalicylic acid. Annatina was thus one of the first patients treated with drug combination therapy. With regard to myself, I contracted a "primary complex" form of TB, localized in the left pulmonary apex with regional lymph node involvement. We both recovered, but were left with a diminished resistance, which rendered the first years of our life together difficult.



Basel, Zeichnung von Emanuel Buchel (Mitte des 18. Jahrhunderts)

3. Postgraduate period (1948-1949)

3.1 Basle

After graduating from medical school in Zurich, I joined the department of experimental pharmacology of the Ciba pharmaceutical company in Basle, under the direction of Professor Rolf Meier. My first experimental study dealt with the regulation of blood pressure via the carotid sinus. Noradrenalin was proven to be the biological mediator. This study served as the "inaugural dissertation" for my medical degree (1949), subsequently published in Arch. Int. Pharmacodyn., vol. 85, pp 399-418. Other non-published studies dealt with the action of antihistaminic drugs on the anaphylactic shock in guinea pigs and the Arthus phenomenon in the rabbit. In the latter, I demonstrated the importance of the biological halflife of a drug, a notion fundamental for drug therapy in patients. I found that a single injection of Phenergan, a long-acting antihistaminic, inhibited the Arthus phenomenon, whereas Anturan, a short-lived antihistaminic, required four injections at six-hour intervals. During this period, I spent a lot of time in the library, where I studied original works in the field of immunology, mostly published in the annals of the Pasteur Institute, where Metchnikof conducted his famous studies and where Metalnikof developed the concept of an immune response against self-constituents of the body. The concept of autoimmunity seemed so absurd that Ehrlich concluded the debate with his famous words, "horror autotoxicus", which subsequently dominated physicians' thinking for more than half a century. Intrigued by the idea that immunity may turn against self-constituents, Annatina and I carried out a series of experiments while recovering from our tuberculosis. We immunized rabbits with homogenized uveal tissue emulsified in the so-called "Freund's adjuvant" (a mixture of heat-killed BCG bacilli suspended in mineral oil and lanolin). Although our rabbits did not develop autoimmune uveitis, we demonstrated that an intraocular variola infection is significantly more aggressive in rabbits sensitized to uvea than in the normal non-sensitized rabbits. We later learned that we had selected the "wrong" species, since in guinea pigs sensitization with homogenized uvea in Freund's adjuvant leads in fact to experimental autoimmune uveitis.

1950 marriage

Guido Constant, 1952

Annatina jr. 1955

3.2 Davos

After our wedding in 1950 in Ftan, Annatina and I spent some time at the pediatric clinic for tuberculous children in Davos. Annatina was heading for a career in ophthalmology and started her training in Lausanne under Professor Bernard Streiff. I was accepted by the clinic of internal medicine (Professor A. Vannotti) six months later. The only relevant research activity in Davos was instigated by a frequent complaint of tuberculous children: hypersensitive skin areas which varied from patient to patient and which were considered by Professor Wissler to be just a weather-dependent rheumatism. Not convinced by this explanation, I examined 93 patients suffering from such hyperalgesic skin zones. In order to objectify the clinical findings, I gave intracutaneous injections of a mixture of acetylcholine and prostigmine into the hypersensitive skin and the contralateral "normal" skin. The two erythematous reactions were evaluated quantitatively by planimetry. The result of these investigations revealed a close relationship between the localization of a tuberculous foyer and the site of the hyperalgesic skin zone (4). This phenomenon had been described by Head 50 years earlier, in patients suffering from gastrointestinal disorders. A few years later, while working in the university hospital in Basle, I applied the findings from Davos to a patient suffering from fever with chills and pain in the right hip and who was already programmed for surgery of the hip. When I examined the patient the afternoon before surgery, I found a hyperalgesic zone in the skin section corresponding to the right kidney. The surgeon, Dr Eggman, was convinced by my argument and changed the surgical preparations from hip to right kidney where he indeed found a perinephritic abscess!

3.3 Lausanne

My three years (1951-1954) at the university clinic in Lausanne turned out to be very rich in clinical and experimental endeavours. Since throughout my career each research project corresponded to a clinical problem encountered in one of my hospitalized patients, I always included the patient in the planning of the experimental approach, thus involving him directly in the investigation of his case. Professor Vannotti was a follower of Claude Bernard, always searching for the cause of a clinical observation. When I asked whether it would be possible to convert two unused garages for my research purposes, his immediate response was to order the conversion of one garage into a rabbit house, the other into a guinea pig stall.

The first patient to trigger a series of investigations was a 68 year-old countryman suffering from chronic idiopathic thrombocytopenic purpura (ITP). This case raised the question as to the mechanism of the low platelet count. On the one hand, the idea expressed by Frank in 1915 of a splenic factor inhibiting the production of platelets still dominated the thinking of clinicians. On the other hand, a number of recent studies supported Kaznelson's hypothesis (1916) that the cause of the low platelet count is a massive destruction of platelets. In 1951, Harrington et al reported that when a transfusion from a patient with ITP was given to a normal person, there was a dramatic fall in the number of platelets in the recipient. I decided to study the effect of the patient's serum on rabbit platelets. The i.v. injection of 4-5 ml of my patient's serum produced a marked diminution of the number of platelets in the rabbit. When 6 ml were injected, the rabbits actually died in an anaphylactic-like state. Splenectomy prevented the lethal outcome of the injection with a much less dramatic fall in the number of platelets. The injection of Phenergan prior to injection of the patient's serum prevented death but not thrombocytopenia. Finally, the absorption of the patient's serum with a large quantity of washed human platelets abolished its capacity to produce thrombocytopenia when injected into rabbits. Splenectomized rabbits were also protected from the action of an i.v. injection of patient serum. Subsequently, I made similar

observations with serum from three other patients suffering from ITP. We could thus confirm the hypothesis of platelet destruction in patients with ITP. The factor responsible for platelet destruction was absorbable on washed normal platelets, suggesting that this factor was a platelet autoantibody (7).

In the same year, I had the opportunity to follow two patients who developed an acute form of thrombocytopenia after ingesting Sedormid. Ackroyd in 1948 conducted a series of in vitro studies which led him to believe that we were dealing with a "partial autoimmune phenomenon", Sedormid acting as a hapten which becomes a full platelet-specific antigen when combined with a platelet component. With Annatina, who was working at the same time in ophthalmology, I carried out a series of experiments which led to the conclusion that we were dealing with a condition similar to serum sickness. The addition of Sedormid to the serum of one patient led to a slight precipitation. The hypersensitivity to Sedormid could be transferred to guinea pigs by the patient serum with occurrence of an anaphylactic pulmonary reaction upon challenge of the animal with Sedormid. We considered it probable that this type of drug-induced allergic thrombocytopenia was due to the action of soluble immune complexes (IC) with a special affinity for platelets. To test the hypothesis that platelets are affected by soluble IC, we conducted a series of experiments with rabbit antihuman serum as well as with human anti-horse serum. We were able to demonstrate that the addition of the corresponding antigen to citrate-anticoagulated blood leads to platelet agglutination and inhibition of clot retraction. We thus concluded that the observations made with the blood of Sedormid-sensitive patient represent a general phenomenon as regards the action of soluble IC on platelets (6). This subject led to a close collaboration with Dr Straessle of the Roche pharmaceutical company. Dr Placidus Platter was the general director of Roche who came to Lausanne to discuss with me the setting up of a close collaboration with his company. In the first collaborative study, we investigated the localization of I-131 labelled human albumin in the various plasma fractions of sensitized and normal rabbits upon intraperitoneal injection of the labeled antigen. We also studied the in vitro affinity of the antigen and the soluble IC on platelets. Following injection of the homologous antigen, IC of different compositions are found in the circulation. The two antigens employed (human albumin, human gammaglobulin) showed different types of behaviour. Soluble IC are concentrated on thrombocytes; some strongly agglutinated normal thrombocytes. These results stressed the importance of soluble IC with regard to their damaging effect on thrombocytes (41).

The discovery of the LE cell phenomenon by Hargraves et al. triggered an avalanche of investigations on the pathogenesis of SLE in general and on the mechanism of the LE cell in particular. With my general interest in immunology, I postulated that an immune mechanism caused the LE cell. Accordingly, in 1952 I attacked the subject and attempted to reproduce the LE cell by experimentally produced antisera. I thus prepared immune sera against human platelets, leukocytes and red cells in guinea pigs. In vitro incubation with human citrated blood showed the phagocytosis of platelets, leukocytes and red cells by neutrophilic, leukocytes and monocytes with the corresponding antisera. No "typical" LE cells could be reproduced (8). The next step included the cell nucleus for the immunization of guinea pigs. The medical biochemistry unit (Drs Jurg Frei and Thérese Béraud) was working on microsomes and mitochondria, discarding the cell nucleus. With Marthe Fauconnet, an outstanding technician with whom I worked for many years, and Thérese Béraud, we immunized guinea pigs with nuclei isolated from human and rabbit cells. The anti-nuclear sera were mixed with human plasma rich in leukocytes, and incubated at 37°C for 30 minutes. The resulting nuclear changes, including immuno-nucleo-phagocytosis, led to the hypothesis that the LE cell is indeed due to an immune mechanism (12). At this very moment, Professor Vannotti called to announce the first patient in the medical department thought to be

suffering from SLE. I immediately performed the LE cell test, which gave a positive result. I then decided to perform absorption tests with isolated cell nuclei which I prepared from 30 ml of blood from a patient with acute leukemia (70,000 myeloblasts/mm3). We were very excited about this experiment which completely abolished the capacity of the LE serum to produce LE cells. Fortunately for our research program, a second patient with subacute SLE was hospitalized a few weeks later which permitted us to repeat the absorption test with another SLE serum, again with a positive result. Electrophoretic examination of the LE serum before and after absorption with isolated cell nuclei showed a considerable diminution of the gammaglobulin fraction, which corresponded to the antinuclear autoantibody thesis of the LE cell factor. At the same time, this result indicates that the LE cell factor cannot be directly responsible for the immunopathology of SLE, since it cannot be absorbed on intact cells, indicating that it does not penetrate living cells. Professor Grabar from the Institut Pasteur, with whom we were in close contact, immediately asked his research fellow, Maxime Seligman, to come to Lausanne to learn the cell separation technique, essential for his own investigations into the immunology of SLE.

Two years later, a third group of investigators, working at the Rockefeller University in New York, invited me to give a lecture on the subject of SLE. Professor Henry Kunkel told me that it had taken him two years to obtain my paper which had been published in a journal not available in the USA. The subject was of great importance to him and our results on the absorption of the LE factor on isolated cell nuclei were fundamental for the pursuit of his own studies with his research fellow, Halsted Holman. The advance I had in my research on the immunopathology of SLE as well as my studies on the action of soluble IC on platelets and leukocytes impressed my American colleagues, resulting in three different offers to join their respective laboratories (Lewis Thomas in New York, Ernest Witebsky in Buffalo and Frank Dixon in Pittsburg).

In 1953, we had on our ward a patient with chronic severe leukopenia (less than 900 polynuclear leukocytes/mm3). Dausset had suggested an autoimmune mechanism for these patients since he found that their serum was capable of agglutinating normal leukocytes. The serum of our patient did indeed produce agglutination of a suspension of normal leukocytes. Since serum from patients with ITP is also active on rabbit platelets, I studied the effect of this patient's serum on rabbit leukocytes. The results of these studies were astounding: the intravenous injection of 3-3.5 ml of this serum per kg bodyweight caused death in rabbits by leukocytic emboli in lungs and kidneys. Absorption tests showed that the addition of normal leukocytes inhibited the action of this serum. After absorption, the beta2and gammaglobulin fractions in the serum of the patient were diminished. The patient was then splenectomized, resulting in an increase in the number of polynuclear leukocytes to more than 1,000; however, the leukocyte specific factor remained in his blood. The spleen appeared enlarged, weighing 270 g. Histological examination showed changes consistent with past tuberculosis of the spleen with no signs of activity. Furthermore, no tubercle bacilli could be found. We concluded that the chronic leukopenia was caused by an autoimmune mechanism, perhaps triggered by the chronic tuberculous process (15).

Continuing our efforts to look for leukoagglutinins, we were struck by the fact that many patients with a positive result were not leukopenic. This observation prompted me to study in detail a strong leukoagglutinin which we detected in a non-leukopenic patient who had contracted tuberculosis and who developed a drug-induced agranulocytosis with severe anemia, requiring various transfusions. His serum only agglutinated leukocytes from 7 out of 22 subjects, unlike the leukoagglutinin of the patient with autoimmune leukopenia, whose serum

agglutinated all leukocytes tested. The agglutination of this non-leukopenic patient was independent of the blood group antigens ABO and Rhesus CDE. Furthermore, this "isoleukoagglutinin" could only be absorbed with the leukocytes of the first blood donor and with the leukocytes agglutinated by this leukoagglutinin.

This serological study proved for the first time the existence of a leukocyte group different from red cell blood groups. Subsequently, Dausset and van Rood attacked the problem of leukocyte grouping, especially since leukocyte grouping looked promising following the observation by Billingham, Brent and Medawar that the induction of immune tolerance with leukocytes also produces tolerance for skin transplants, suggesting that leukocytes contain important tissue-specific isoantigens. Indeed, HLA (human leukocyte antigen) matching has become of major importance in the practice of tissue transplantation.

During the years 1952-1953 I was confronted with a new clinical problem (7). This problem concerned male patients presenting a clinical picture with signs of vasculitis, vascular purpura of the Schoenlein Henoch type, migratory superficial phlebitis, sometimes also affecting medium-sized veins, painful subcutaneous nodules and visceral symptoms (splenomegaly, signs of glomerulonephritis). The disease was intermittent in character in all patients and most manifestations were of limited duration (5-10 days). Most attacks of disease activity were accompanied by high fever and an ESR of over 60 mm/hour. All these patients presented signs of a severe bacterial hypersensitivity against strepto- or staphylococci, with repeatedly negative blood cultures. The histology of the purpuric lesions showed severe perivascular inflammation with neutrophils, leukocyte fragments, and a variable participation of eosinophils. In addition, some arterioles showed foci of fibrinoid necrosis. Positive skin tests with bacterial vaccines showed a very similar pattern of vasculitis. There was kidney involvement in 4 of the 7 patients, with microhematuria, mild proteinuria and cylinduria. In these patients, we detected infectious foci in various areas, e.g., sinusitis, dental foci, bronchiectases. In each case we prepared an "autovaccine" from the respective foci which, applied intradermally, produced a strong skin reaction in all the patients. We were able to do additional tests in one patient with chronic infection of a wound resulting from a fall from a scaffold. This patient suffered from frequent attacks of vascular purpura with kidney involvement. He reacted very strongly when injected with either staphylococcal vaccine or with autovaccine. We decided to study the patient's immune state using the Prasnitz Kustner procedure (passive transfer of the hypersensitivity state). A friend of the patient offered to serve as recipient for this transfer and was first tested with staphylococcal anatoxin. At a dilution of 1:10, 0.2 ml of this vaccine produced, after 18 hours, a 5 mm diameter papule. For the passive transfer test, we prepared a leukocyte suspension of 250,000 leukocytes/mm3 from the patient (by differential centrifugation), which was washed twice before being used for the experiment. The recipient was prepared by a subcutaneous injection of 0.5 ml of the patient's serum in the right forearm, 0.5 ml of the leukocyte suspension in the left forearm. Twenty-four hours later, 0.2 ml of the 1:10 diluted staphylococcal anatoxin was injected into the two prepared sites. The result, read 24 hours later, was impressive. At the site prepared with the patient's leukocytes, a severe inflammation appeared with an erythematous oedema measuring 15 x 6 cm. On the other forearm prepared with the patient's serum, the injection of the diluted anatoxin also produced a positive reaction but far less severe (erythematous swelling measuring 2-3 cm in diameter).

These patients did not suffer from a systemic infection with living microbes but presented signs of hypersensitivity to bacterial products, with involvement of various organs. They are thus suffering from a

disease belonging to the group of "collagen diseases". Indeed, in 1942 Klemperer coined this term without claiming a similar etiopathogenetic pathway for all of them (267). These 7 patients did not suffer from an autoimmune disease, but from a "serum sickness"-like condition. However, this does not preclude the use of immunomodulating drugs. In these patients, the pathogenic pathway belonged predominantly to cellular immunity, thought at the time to be due to cell-bound antibodies reacting with the same antigenic structure as humoral antibodies. Today, we know that the antigenic target is actually different from that recognized by antibodies. Most of our patients developed both cellular and humoral immunity; I suppose that the latter led to immune-complex nephropathy, similar to IgA nephropathy.

I continued to study patients suffering from this type of collagen disease during my stay in Basle. On my father's 70th birthday, this topic was brought up, much to his interest as it was he who had actually coined the term "microbid" to designate eruptions based on bacterial hypersensitivity and showing, on histological examination, perivascular infiltration with leukocytes or leukocyte fragments, as well as foci of fibrinoid necrosis. I published 11 additional cases of patients suffering from this type of vasculitis (60). In 9 of these patients, I studied the transferability of the hyperergic state into a normal control, always a friend of the patient concerned. The eagerness of the patients and their respective friends to understand the disease better was incredible. At the time, hepatitis B and C had not yet been recognized and we tested just the liver function in all patients and volunteers for the transfer studies, and for syphilis. In all 9 patients, we transferred the delayed type of hypersensitivity using the respective bacterial antigen (7 times staphylococcal, streptococcal in one patient, E. coli in one other). In two patients, in addition to the delayed type reaction, we also detected an immediate urticarial reaction at the site prepared with the patient's serum. In two cases, we studied the passive transfer with vital and killed (3x frozen and thawed) leukocytes. Only vital leukocytes gave a positive delayed type hypersensitivity reaction, similar to the results obtained by Landsteiner and Chase in guinea pigs (J. exp. Med. 71: 2371, 1940).

Our studies on the effect of soluble IC on platelets and leukocytes caught the attention of Placidus Plattner, member of the board of directors at Hoffman-La Roche, and Professor Juergens, then director of research at the same company in Basle, because of their interest in drug-induced blood dyscrasias such as Sedormid purpura and aminopyrine-induced agranulocytosis. Research on this subject had been very scarce and unproductive. Dr Plattner and Professor Juergens visited me in Lausanne with a proposal to fund a research laboratory at the Basle University Policlinic of Medicine. Professor Juergens was a close friend of Professor Gsell, director of the policlinic. With our (mine and Annatina's) consent, Prof. Juergens initiated the negotiations which resulted in my appointment as chief resident in charge of research at the policlinic, including participation in clinical activities with patients. While still working in Lausanne, I ordered the equipment necessary for my research activity in Basle, in particular a cold-centrifuge (in those days a rare instrument) and a scintillation gamma-counter for studies with radioactive isotopes. In autumn 1954, we moved to Basle with our little son, Guido Constant, born on 10 March 1952. Annatina joined the Basle Ophthalmology Clinic and I organized the new research facilities with the help of two technicians, Cecile Zuber and Hans Bragatsch.

3.4 Basle (1954 - 1958)

One of the first projects in Basle concerned the fate of erythrocytes from "birth to the grave". This study was carried out at the invitation of the International Committee of the Society of the Reticuloendothelial System (RES) to report on this subject on the occasion of their first symposium. The meeting took place at the Chateau de Royamont in France in June 1955. Since at that time little was known about the elimination of old red cells, we conducted a series of experiments in guinea pigs and rabbits. We studied the elimination of fresh erythrocytes labeled with Cr51, and erythrocytes aged in vitro. The site of destruction of aged red ells was determined by measuring the concentration of chromium51 in various tissues of the animals 25-35 days after injection of in vitro aged red cells (44). The rate of red cell elimination was shown to depend on their age. These erythrocytes were eliminated throughout the RES by phagocytosis of red cells or red cell fragments, without prior hemolysis. The distribution of radiochromium varied with the age of the injected red cells. Rapidly eliminated old red cells accumulated predominantly in the spleen and liver; slowly eliminated cells (half-life of more than 14 days) showed a predominant elimination within the bone marrow. Splenectomy had no effect on red cell survival in the normal animal. These results elicited the interest of many hematologists. In particular, Georg von Hevesy visited me in Basle, impressed by the results we had obtained. Ehrenstein and Lockner confirmed our results (Nature 181: p. 911, 1958).

The next study on the RES concerned the pathogenesis of hypersplenism. With the new technique of labelling red cells with Cr51, we found a shortened red cell life span in all patients presenting the clinical syndrome of "hypersplenism" (46). In animal experiments, I used two methods to produce hypertrophy of the splenic RES: 1) implantation of Percorten tablets (an anabolic steroid) into the spleen of rabbits; 2) tuberculous infection of the spleen in guinea pigs (33,52). In both instances, red cell survival was diminished with an increased uptake of Cr51 in the spleen. Three rabbits were sacrificed 40 days after injection of labelled erythrocytes. The amount of chromium was 6-25% in the normal rabbits, 23-45% in the Percorten-implanted animals. Splenic smears showed phagocytized red cells or red cell fragments within histiocytes. We thus concluded that the mechanism of hypersplenism involves an increased elimination of normal red cells by splenic histiocytes, due either to hypertrophy of the splenic RES or to hemodynamic factors (e.g. hypersplenism in patients with portal hypertension).

I also continued to work on the role of soluble immune complexes (IC) in the production of leuko- and thrombocytopenia, taking advantage of the possibility of labelling proteins with I-131 (22). In a first series of experiments, we studied the effect of antigen-antibody reactions upon rabbit thrombocytes in vivo with human serum albumin as antigen. For the in vitro experiments, plasma of rabbits sensitized with human gammaglobulin was used as antibody, I-131 labelled human gammaglobulin as the antigen. The following results were obtained:

Following injection of the homologous antigen, antigen-antibody complexes were found in the circulation of the sensitized animals. They were localized not only in different plasmafractions, but also exhibited different biological properties with regard to their effect upon thrombocytes and leukocytes of normal rabbits. Soluble IC are strongly fixed on thrombocytes. The extent of binding depends upon the degree of sensitization and upon the antigen to antibody ratio. In fact, the mode of action of such IC depends upon the nature of the antigen, the antibody and the ratio of the two (41). Similar results were obtained with leukocytes. The in vitro fixation of labeled IC varied according to the proportion between antigen and antibody. In vivo- prepared IC obtained upon

intraperitoneal injection of radiolabelled albumin were found in different plasma fractions. The action of the IC depends on the antibody, the antigen, and the relative composition of the IC (49).

To make the bridge between these studies on IC with a protein as antigen, we were interested in conducting similar experiments with simple chemical non-protein compounds. One of my students, A. Pearl, used two different compounds, picryl chloride and arsphenamine emulsified in Freund's adjuvant for the immunization of rabbits. No positive results were obtained with picryl chloride. In two out of five rabbits immunized with arsphenamine, the plasma produced a strong agglutination of platelets and leukocytes only in the presence of arsphenamine, thus simulating results obtained with the serum of patients with Sedormid-thrombocytopenia and with the serum of patients who recovered from aminopyrine-agranulocytosis (77). In view of these studies on the role of IC on platelets and leukocytes, I was invited to organize a colloquium on drug-induced allergic blood dyscrasias at the 5'h European Congress of Hematology in Freiburg, Germany in September 1955.

During the 1950s, an increasing number of patients attending the Medical Policlinic (outpatient department of medicine) presented signs of kidney damage. These patients suffered from chronic cephalea and had been taking phenacetin-containing analgesics for many years. Histological examination of kidney biopsies revealed signs of interstitial nephritis (IN). Most of the patients also presented signs of urinary tract infection. At the time, most clinicians blamed phenacetin as the cause of IN, but with no experimental proof. I was thus motivated to investigate this syndrome in experimental animals. For this purpose, we gave 16 rabbits incremental doses of Saridon (phenacetin, isopropylantipyrine, Persedon and caffeine) for an 8-month period, during which two animals died.

After 7.5 months, 7 of the remaining animals were given i.v. injections of E. coli every other day for a two-week period. A third group of non-pretreated rabbits only received E. coli injections. Eighteen days after the E. coli treatment, all animals were sacrificed (70). All the animals pretreated with Saridon and challenged with E. coli presented histological signs of IN. In 4 of the 7 animals thus treated the IN was quite severe, and they also showed signs of kidney damage with increased levels of blood urea nitrogen. In the animals of the Sedormid without E. coli group and in the E. coli without Sedormid group, the kidneys showed no signs of IN. We concluded that prolonged "abuse" of large doses of Sedormid or other phenacetin-containing analgesics renders the kidney vulnerable to infection with otherwise non-pathogenic bacteria, resulting finally in the development of interstitial nephritis (70). In addition to its renal toxicity, phenacetin is also toxic for erythrocytes: red cell survival is diminished in animals receving phenacetin as well as in patients abusing phenacetin-containing analgesics (71).

In Basle, I continued to work on the serology of systemic lupus erythematosus (SLE). Since the LE factor can be absorbed on isolated cell nuclei, I applied this principle to the development of a diagnostic test. Cell nuclei fix the LE factor upon incubation with LE sera, which then remains fixed after "washing procedures". The nuclei coated with the LE factor, a gammaglobulin, react with an anti-human gammaglobulin serum, thus consuming its agglutinating capacity of anti-D-coated erythrocytes. This test, called the antiglobulin consumption test, proved to be a very sensitive method for the detection of antinuclear antibodies (36). We then applied the passive hemagglutination test to the detection of various antibodies: tanned sheep erythrocytes were coated with the following antigens: nucleoprotein, DNA and RNA. Three out of 5 sera from patients suffering from a mild form of SLE gave a positive result with thymonucleoprotein, but also with DNA. This test was highly

reproducible with red cells from different sheep (58). With this simple test, we thus discovered that SLE sera not only react with isolated cell nuclei, but also with the main constituents of the nucleus, nucleoprotein and DNA. Upon absorption with nucleoprotein, the sera lost the capacity to produce LE cells; upon absorption with DNA, the sera were still capable of producing LE cells, but with a slightly different morphological appearance.

In 1956, Singer and Plotz reported on the latex fixation test for the detection of the rheumatoid factor. We also successfully used this technique to detect antibodies against DNA and nucleoprotein and reported our findings at the third international Congress of Allergy in October 1958 (74). For the serological screening, we then used the antiglobulin consumption test with cell nuclei, and the latex agglutination test with DNA, nucleoprotein and gammaglobulin. The antiglobulin consumption test with cell nuclei was invariably, and very markedly, positive with sera from patients with SLE. In patients with rheumatoid arthritis showing a positive LE cell phenomenon, the latex agglutination test with nucleoprotein was positive in only 7 out of 100 cases, while in 28.5% of these sera the antiglobulin consumption test with cell nuclei yielded only very weakly positive results. From these results it was concluded that the two collagen diseases, SLE and RA, exhibit different serological patterns, but are closely connected.

The discovery of the rheumatoid factor raised the question as to its role in the pathogenesis of RA. In 1956, I had occasion to take care of a female patient with RA in its initial phase. During this early period of the disease, the latex agglutination test with aggregated gammaglobulin was repeatedly negative; the patient first tested positive five months after testing began. To investigate whether this factor alters gammaglobulin turnover, we studied the disappearance rate of radio-labelled autologous gammaglobulin in a patient with a positive latex fixation test and in a negative control person. The disappearance rate was found to be the same in the patient and the control, suggesting that the rheumatoid factor is after all a secondary phenomenon with no causal role in RA (79). I reported on the serological findings in patients with SLE and RA at the 7th Congress of the International Society of Blood Transfusion in Rome, 1958 (85).

4. Entering the Global Scientific Community

During my time in Basle I was invited to many international meetings to report on the results of my research activities. Of special relevance was an invitation to give a main lecture at the Boston Congress of the International Society of Hematology in September 1956, followed by a lecture tour in the USA.

In 1955, the Thieme publishing company asked me if I would compile a textbook on "Immunopathologie in Klinik und Forschung". I accepted to prepare the textbook in collaboration with Karl Otto Vorlaender and together we started to correspond with the leading experts in this vast new domain. The book was published in 1957, was translated into French and Spanish, and proved to be a great success.

In November 1956, I received a visit from Mr Froistad from Boston who had organized the Royamont conference on the RES. He asked me to organize an international symposium on a topic of my choice. I hesitated at first, but finally accepted as it would give me the opportunity to bring together all the experts in this new field of clinical immunology. I decided to assume the function of secretary of this symposium on immunopathology and chose a well-known scientist and friend, Professor Pierre Grabar of the Institut Pasteur in Paris, to be president of the symposium. Mr Froistad agreed to this arrangement. I set up a tentative programme

and started to invite the proposed speakers. Without exception, they all accepted to participate at this first ever meeting on this topic. Annatina and I decided that the meeting would start in Basel and then move to a "remote" place in the heart of our home country, Seelisberg - the "cradle" of the foundation of Switzerland in 1291 - for the main part of the symposium.

The Swiss Academy of Medical Sciences co-sponsored this meeting (my research was supported in part by the Academy who covered the salary of one of my technicians, Marthe Faudonnet).

The first session of the symposium took place at the "Vesalianum", where Johannes Friedrich Miescher had taught physiology. The opening ceremony and evident generosity of the Canton and City of Basle impressed all the participants. During this first session in Basle, leading experts (E. Witebsky, R.R.A. Coombs and P. Grabar) developed the concept of immunopathology and the question of whether immune reactions against "self tissues" really do exist. After a generous lunch in the Wildt's house (where the His family had lived), Pullman cars were waiting to transport the participants from Basle to Seelisberg. At this mountain resort, there was nothing to distract the participants from their discussions about their various research activities. Many close associations between the scientists emerged from this symposium. After the final session, the Pullman cars were ready to transport the participants to Lucerne.

This extract from the scientific programme of the symposium gives an idea of activities in clinical immunology at that time:

Peter His III.,Guido A. and Peter A.Miescher

1958, Roma, Peter A. and Annatina

Scientific Programme

Monday, 23 June, Inaugural meeting in Basle, Vesalianum
Chairmen: O. Gsell (Basle) and P. Grabar (Paris)

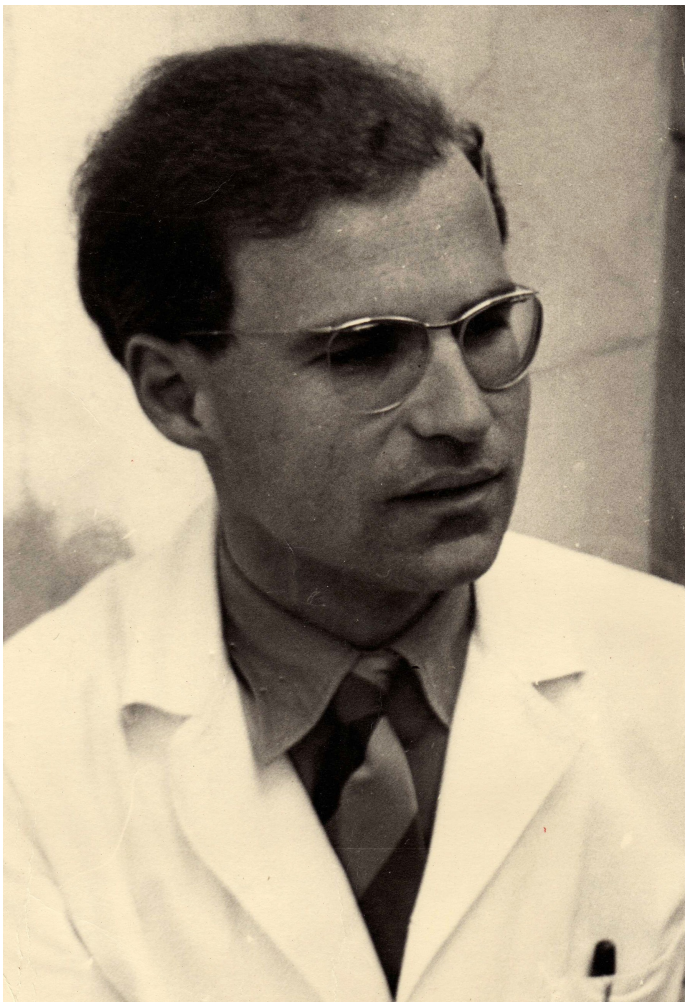
Opening of the symposium by the President, Prof. Pierre Grabar (Paris).
Welcome addresses by the President of the Swiss Academy of Medical Sciences,
Prof. A. Gigon (Basle) and the Dean of the Medical Faculty, University of Basle, Prof. Karl Berhard.

E. Witebsky (Buffalo) : Historical roots of present concepts of immunopathology.
R.R.A. Coombs (Cambridge) : Concepts and mechanisms of pathogenic immunoreactions.
P. Grabar (Paris) : The problem of auto-sensitisation.
H. Isliker (Berne) : The properdin system and its significance for immunopathology.
R.A. Good (Minnesota) : Studies on agammaglobulinemia and hypogammaglobulinemia.
S. Barandun (Berne) : Discussion on the antibody-deficiency syndrome.

Tuesday, 24 June, Seelisberg
Organ-specific immunopathology
Chairmen : F. Dixon (Pittsburgh) and E. Letterer (Tubingen) Et cetera.

At the end of the symposium, it was decided to set up an international committee whose function would be to organize every year a symposium on immunopathology. For the first symposium, scientific presentations were accepted in English, French or German. For the subsequent 8 symposia, however, it was decided to have presentations in English only. Robin Coombs charmingly remarked that it was impossible for an Englishman to speak in any other language but English, while he could see that all the non-English participants were quite fluent in English, which prompted this decision.

After the Seelisberg symposium, the Prague Academy of Science invited 12 scientists to a meeting held in Prague's beautiful castle. The country was still under communist rule and our Czech colleagues were very careful not to engage in political discussions. The following incident illustrates the political atmosphere. One morning, Frank Dixon and Robert Good were discussing the quality of hotels in Switzerland and in Prague, and it was mentioned that, in Switzerland, a basket of fruit, a bottle of mineral water and flowers were put in all rooms. To their surprise, that same evening all these items appeared in their rooms. We understood that we were being very closely monitored by hidden microphones.



Herrn Prof. Dr. Peter Miescher

Der Regierungsrat des Kantons Basel-Stadt
verleiht Ihnen auf Antrag der Kommission für die Verleihung
des Wissenschaftspreises der Stadt Basel in Anerkennung Ihrer
wissenschaftlichen Verdienste auf medizinischem Gebiet und Ihrer
erfolgreichen Bestrebungen zum Wohle der Kranken den

Wissenschaftspreis der Stadt Basel
fur das Jahr 1963.

Einer Basler Gelehrtenfamilie entstammend, haben Sie sich nach medizinischen Studien und klinischer Ausbildung fruhzeitig der wissenschaftlichen Forschung zugewandt and im Jahre 1957 an unserer Universitat die Venia docendi fur innere Medizin erworben. Ausgehend von klaren klinischen Fragestellungen and vertraut mit den modernsten experimentellen Methoden, gelangen Ihnen wichtige Beitrage zur Deutung and Aufklarung immunbiologischer Vorgange.

5. NEW YORK

The year 1959 brought a radical change to my career as well as to our family life. I first of all spent six months as visiting professor at New York University while the family remained in Basle. Annatina was running a very successful private practice in ophthalmology. We hesitated to leave Switzerland and initially rejected-the offer from the NYU to join the faculty as full professor of medicine with tenure from the very beginning. However, when we compared the research activities at the NYU with those in Basle, and considering the fact that I was quite isolated with my research activity at the medical policlinic, we gradually became inclined to accept the offer of a full professorship. During this first period of "separation", Annatina realized that I was quite unable to live alone. Our friends, Annette and Baruj Benacerraf, wrote Annatina an alarming letter, begging her to come to New York. She thus decided to come to New York with the children and the housekeeper in order to reunite the family. She was received enthusiastically by our friends at the NYU, and was soon asked to participate in the teaching program of second-year students as "instructor of medicine".

In August 1960, the whole family settled in New York City. Soon we all realized that we were not really in the USA or just in New York, but that we had joined the "whole world" of those days. Our children were enrolled in a day-school called the "Lycée francais de New York" where they soon spoke several languages and met children of all possible skin colour from around the globe, although they were in the main children of diplomats assigned to New York for a limited period of time.

As for our everyday life, we had to rapidly learn non-scientific and non-medical English. We invited a young teacher from the Lycée francais, Martine Ventré from Montpellier, to come and live with us as French had to be the main language for our two children. We had the good luck to live on the 11th floor of 21 East and 90th Street, overlooking Central Park with its drinking-water lake. This wonderful apartment with 7 rooms and 3 bathrooms became our home for the next eight years. With the exception of some rats in the cellar, we never had intruders of any other kind, but we did have hundreds of visitors as we were within easy reach of the center of Manhattan, the schools and subways, and just a short drive from NYU Bellevue Hospital and several wonderful fish markets and supermarkets.

In New York City in the sixties, our global involvement expanded as we started to acquire items not strictly essential for our daily needs, such as antique French provincial furniture. We also bought a pair of gothic stone lions and a sculpture of a saint, sold at "the pound" (today, here in Urbino, Italy, we still enjoy a Regency chest of drawers from those days 40 years ago in New York). As for chinaware, the beautiful English things were so much appreciated by the white, Anglo-Saxon protestant (WASP) community that they were out of our price-range. We thus turned to blue and white China-town items, and to solid Japanese copies of post-world war II Meissen dishes by the dozen, very inexpensive and so robust; we still enjoy them daily on our table (also blue and white, and labeled "Blue Danube"). Our passion for all things Chinese had begun.

After a few months, we lost our housekeeper. She married a wonderful Austro-American and soon joined the "jet-set".

With regard to our professional lives, I had the task of setting up a new hematology division within the department of medicine. Lewis Thomas was the very efficient chairman of the department and an eminent scientist (he later became president of the Sloan Kettering Institute). Our division gradually became one of the

leading hematology services in New York. Alan Johnson, associate professor of medicine, was in charge of coagulation and hemostasis with a large group of collaborators including Marjory Zucker, associate professor and expert in thrombocyte function. She was one of the first investigators to assess the effect of aspirin on platelet adhesion. Professor Robert Silber was in charge of biochemistry and Professor Ed Amorosi in charge of blood cell kinetics.

I also had to assume the role of architect for the construction of additional research and teaching laboratories. For advanced medical students, we set up a "home laboratory" for special scientific work. Once the new hematology division was operational, we applied to the NIH for a large grant for teaching and training in hematology. Our application was successful and provided us with the funds necessary for this purpose. In addition, every independent investigator in the division was funded by special grants from the NIH and from private funds. Annatina was responsible for organizing the course on clinical pathology for 115 second-year students. Enrolment of students at the NYU was very selective; out of more than 3,000 candidates, only 115 were accepted!

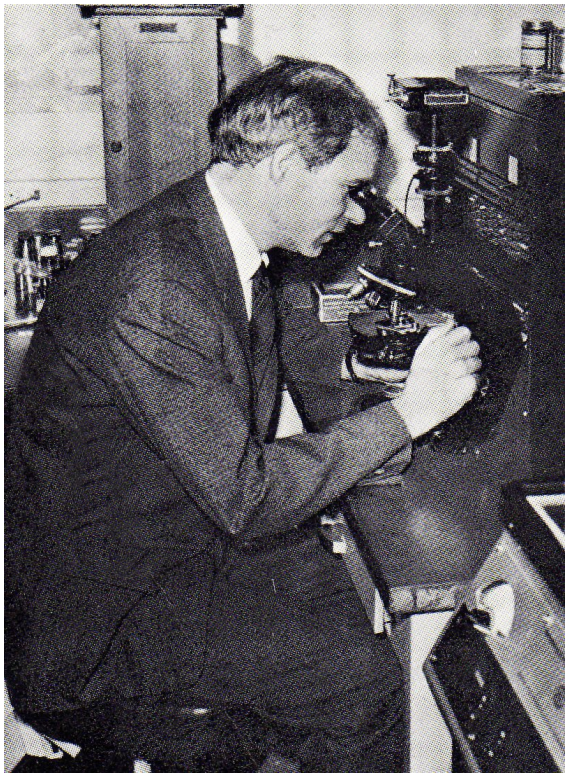
Every summer, students from the NYU visited us at our Swiss home in the Engadine.

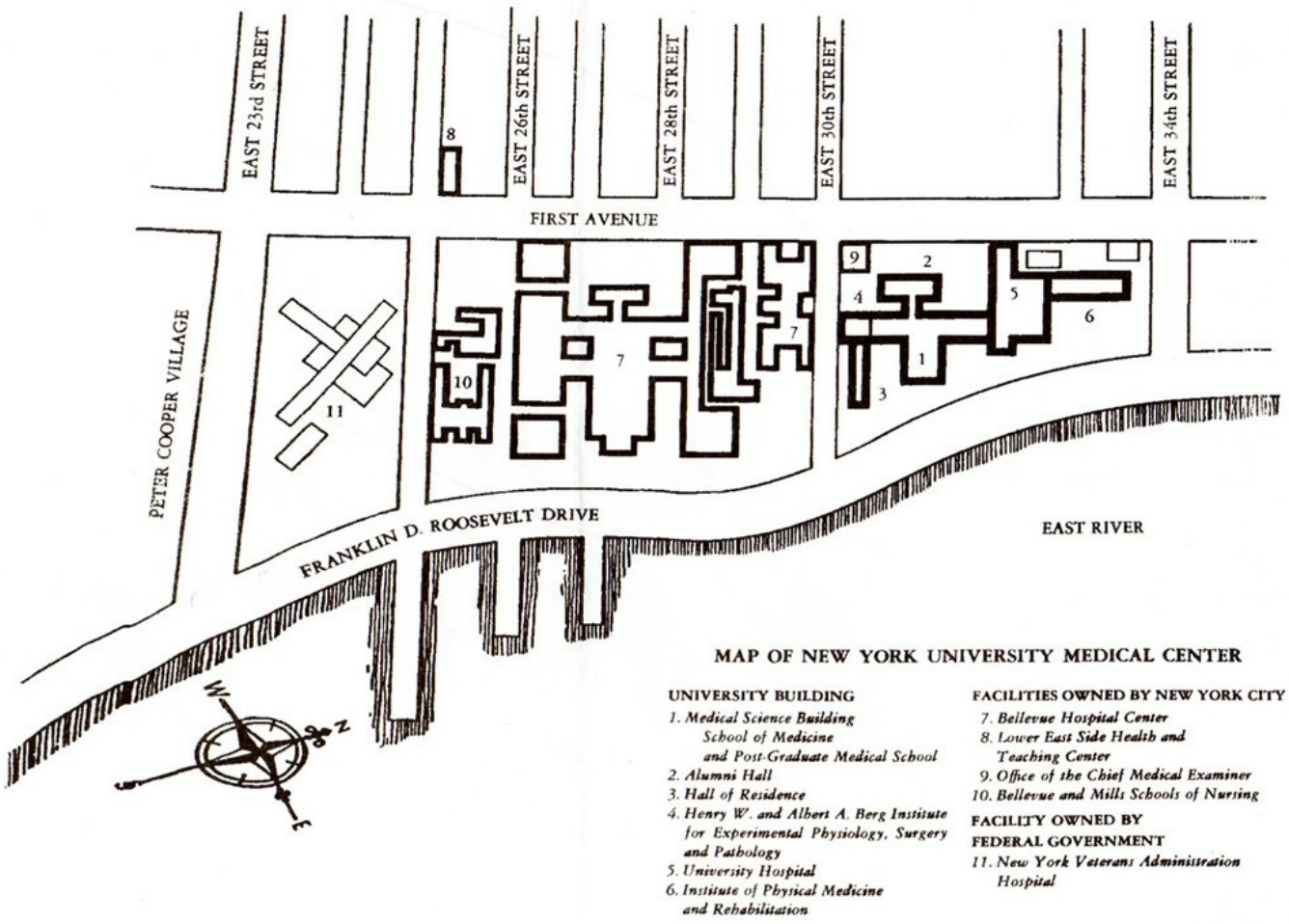
Concerning my scientific activity, I was fortunate to be able to collaborate with outstanding scientists such as Baruj Benacerraf from NYU who later received the Nobel prize for his discovery of the immune response genes, which turned out to be fundamental for the development of autoimmunity as well as for organ transplantation. Other outstanding scientists with whom we collaborated were Henry Kunkel from the Rockefeller University, Hans Popper from the Mount Sinai School of Medicine and Ed Franklin from NYU.

In addition to my research activity, I was working as a clinician with the residents on the wards as well as with special private patients. NYU actually required the professorial staff to engage in private practice in order to better assess the direct and personal responsibility of the physician towards patients.

One of my first studies in New York dealt with the immunopathology of lupus erythematosus in animal experiments. In intense immunization programmes, nucleoproteins were found to be weak antigens in rabbits and guinea pigs. The resulting antibodies reacted with nucleoprotein and/or DNA and histone. There was interspecies cross-reactivity. Only one guinea pig immunized with nuclei showed a weak Feulgen positive LE-like phenomenon. The serological pattern of anti-nucleoprotein antibodies in these experimental animals was strikingly similar to that in SLE patients. No pathologic changes pathognomonic for SLE were observed in any of the animals. Thus, these antibodies did not seem to be pathogenic for the experimental animals (94).

With Norman Cooper, associate professor of pathology at NYU, I continued to investigate immune complexes. Soluble IC had been prepared with rabbit anti-ovalbumin serum and three times recrystalized ovalbumin. These complexes, prepared in slight antigen excess, were shown to agglutinate rabbit platelets. With the aid of the fluorescent antibody technique, fixation of the IC upon the agglutinated platelets was demonstrated (91,95).





MAP OF NEW YORK UNIVERSITY MEDICAL CENTER

UNIVERSITY BUILDING

1. *Medical Science Building School of Medicine and Post-Graduate Medical School*
2. *Alumni Hall*
3. *Hall of Residence*
4. *Henry W. and Albert A. Berg Institute for Experimental Physiology, Surgery and Pathology*
5. *University Hospital*
6. *Institute of Physical Medicine and Rehabilitation*

FACILITIES OWNED BY NEW YORK CITY

7. *Bellevue Hospital Center*
8. *Lower East Side Health and Teaching Center*
9. *Office of the Chief Medical Examiner*
10. *Bellevue and Mills Schools of Nursing*

FACILITY OWNED BY FEDERAL GOVERNMENT

11. *New York Veterans Administration Hospital*

PETER A. MIESCHER, M. D.
PROFESSOR OF MEDICINE
NEW YORK UNIVERSITY SCHOOL OF MEDICINE

TEL. OR 9-3200
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550 FIRST AVENUE
NEW YORK 16, N. Y.

The City Of New York

In recognition of his scientific ability

Peter A. Miescher

is appointed

Health Research Council Career Scientist

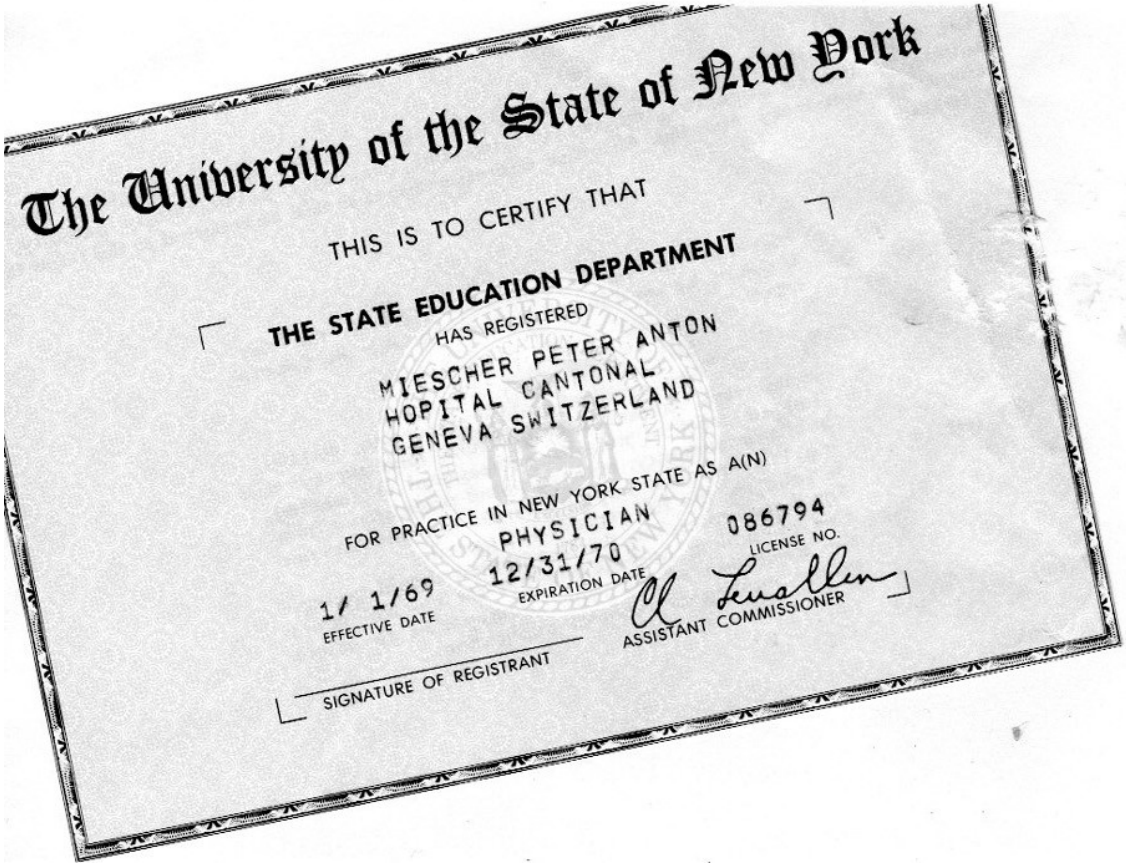
to enable him to pursue a career in research and to contribute to the health and welfare of the citizens of New York.

Date: July 1, 1960

Robert F. Wagner
Mayor

Louis Baumgartner M.D.
Commissioner of Health

Colin M. MacLeod
Chairman, Health Research Council



The University of the State of New York

THIS IS TO CERTIFY THAT

THE STATE EDUCATION DEPARTMENT
HAS REGISTERED
MIESCHER PETER ANTON
HOPITAL CANTONAL
GENEVA SWITZERLAND

FOR PRACTICE IN NEW YORK STATE AS A(N)
PHYSICIAN

086794
LICENSE NO.

1/ 1/69
EFFECTIVE DATE

12/31/70
EXPIRATION DATE

ASSISTANT COMMISSIONER

SIGNATURE OF REGISTRANT

One particular type of IC disease concerns mixed IgM-IgG cryoglobulinemia (142). During the initial years in New York, we observed a few patients with purpura of the vascular type and arthralgia in whom we found a very low C2 complement level. Histological examination of purpuric lesions showed a severe vasculitis with heavy deposits of complement and immune globulin (141). The serum of these patients produced a heavy precipitate after incubation at 4°C, which dissolved again when the temperature was raised to 37°C. Lo Spalluto initially described this type of mixed cryoglobulins with a specific "rheumatoid" type of IgM reacting with any IgG at cold temperature. We were tempted to conclude that this type of IC vasculitis occurs upon exposure of the patient to cold temperature. One of our patients suggested spending one hour in the cold room (4°C) two hours after injection of a radiolabelled C2 complement component prepared by Hans Muller-Eberhard for this purpose. To our surprise, there was no accelerated disappearance rate of C2 and the patient did not develop a single purpuric lesion. Questioning the patient about possible trigger factors, she told us that she developed a purpuric rash every time she consumed milk products. Another patient (a female physician) suffering from mixed cryoglobulinemia informed us that she developed a purpuric rash every time she ate oysters. In all these patients the histology of the purpuric lesion was identical (vasculitis with heavy deposits of Ig and C). We thus postulated a two-step pathology with an allergic vascular reaction triggering the "rheumatoid cold factor" which in turn triggers complement interaction and the resulting inflammation. At that time, the hepatitis C virus had not yet been discovered. Ten years later, it turned out that 90% of patients with this type of mixed cryoglobulinemia were HCV positive. Furthermore, 20 years later we demonstrated the role of HCV in one of our patients that we had treated for 8 years without success. This patient became HCV negative upon treatment with alfa-interferon + Ribavirin, but also negative with regard to her cryoglobulin: complement levels returned to normal, tests for cryoprecipitation remained negative and she no longer developed purpuric lesions. Today, years later, she has developed rheumatoid arthritis and finally a "conventional" rheumatoid factor, without precipitating IgG at cold temperatures. This patient perhaps has a special genetic predisposition to autoimmunity.

In contrast to the immunohistological findings in our patients with mixed cryoglobulinemia-purpura, it seemed relevant to study the purpuric lesions of the Schoenlein-Henoch type, i.e. in patients where we had previously found a delayed type of hypersensitivity reaction against microbial antigens (60). The two patients with this type of vasculitis where we performed a skin biopsy showed the following immunohistological picture: at the site of a "leukoclastic vasculitis", we could only detect deposits of fibrinogen, but no trace of immunoglobulin or complement (41). These results confirmed our prior conclusion that the Schoenlein-Henoch purpura represents a cellular (delayed) type of immunity (60).

A series of experiments at the NYU dealt with the mechanism by which sensitized bacteria (96) and antibody-coated red cells are eliminated by the RES (117,120,123). These experiments were conducted mainly by Hans Spiegelberg, whose fascination with these projects stemmed from his work with me in Basle on the role of nuclear constituents in the LE cell phenomenon (109). We were able to demonstrate the role of complement in the immune clearance of sensitized E. coli and sensitized rat erythrocytes in mice. Complement depleted animals were no longer able to rapidly eliminate antibody-coated E. coli and rat erythrocytes from the blood. After preincubation with fresh serum, these elements were again cleared in the complement-depleted mice (117,120,123). Pepsin- and papain-digested antibodies completely lost their hemolytic and opsonic, but not agglutinating, activity. Even red cells strongly agglutinated by pepsin- or papain-treated antibodies, survived normally in complement-depleted animals (123).

With regard to the role of complement in immune hemolytic anemia in the human, we studied the mechanism of red cell destruction in a case of cold agglutinin-mediated hemolytic anemia. A gamma-1 macroglobin produced agglutination of compatible red cells at 4°C, and hemolysis in the presence of complement at a temperature of 20°C. This cold agglutinin is easily and quantitatively eluted from the red cells. If the reaction is done in the presence of complement, the cold agglutinin is still easily eluted, but non-hemolytic complement components remain fixed on the surface of red cells, leading in vivo to a shortened red cell survival with preferential elimination of the complement-coated cells from the blood by the RES of liver and spleen (114). It thus could be concluded that the presence of antibodies, upon fixation of complement, is no longer necessary for the elimination of complement-coated red cells by the RES.

Another series of experiments dealt with experimental thyroiditis. We selected this model to investigate the relative roles of cellular and humoral immunity in the pathogenesis of autoimmune thyroiditis. Use was made of the fact that when minimal amounts of the immunizing antigen are heavily conjugated with a hapten, serum antibody production is decreased without interfering with the development of delayed-type (cellular) hypersensitivity. Two groups of guinea pigs were immunized with genuine, respectively picrylated, thyroglobulin in Freund's adjuvant. The incidence of thyroiditis and the incidence of delayed skin thyroglobulin reaction were positively correlated, while no such correlation between thyroiditis and circulating antithyroglobulin antibody was apparent (106). This result may corroborate the clinical observation made in various autoimmune diseases that disease activity does not depend on the respective autoantibody titres.

In studies conducted in collaboration with Hans Spiegelberg, we used this model of experimental autoimmune thyroiditis in guinea pigs for the evaluation of immunosuppressive drugs. In particular, we tested the antimetabolites 6-mercaptopurine (6MP) and methotrexate (MTX) during the immunization phase as well as in already immunized guinea pigs that had developed thyroiditis. Both compounds depressed delayed hypersensitivity to thyroglobulin and immune thyroiditis. Antibody formation to thyroglobulin was strongly depressed by MTX but was not significantly influenced by 6MP.

At the time we showed the strong immunosuppressive activity of MTX in guinea pigs, we had on our ward a patient with a fulminant course of SLE. This patient was under long-term 6MP medication, initially with apparent good results but now totally resistant. She had had a high fever with chills for the past 5 days with no evidence of infection. I decided to treat her with MTX i.v. at a dose of 100 mg (with ample hydration), a dose well supported by our leukemia patients. The injection was well tolerated by the patient and in less than 24 hours she became afebrile and two days later could be discharged. After one week, the fever returned but she again responded to 25 mg of MTX. We continued to use MTX for lupus patients and found that 15 mg i.v. or i.m. are sufficient, the effect lasting 6-7 days. Orally administered MTX was not effective in cutting lupus-fever. Methotrexate turned out to be one of the most efficient immunosuppressive drugs at that time, with little associated toxicity if given every other week and if 5 mg of folic acid per day is administered for 3 consecutive days post MTX injection. I discussed our results with Murray Bornstein, professor of neurology at the Albert Einstein Medical College who was also using 6 MP for the treatment of multiple sclerosis. He was facing a similar problem: one of his patients who had initially been doing well on 6MP, had a recurrence of her neurological disease despite a gradual increase of 6 MP to 150 mg per day two years after starting 6MP medication at dose of 50 mg per day (150 mg as an initial dose would cause significant toxicity). We concluded that patients gradually become resistant to this antimetabolite, which loses not only its toxicity but also its

efficacy in terms of immunosuppression. After the first 3 months of using MTX, we learned about its "late toxicity" in patients receiving this drug every week. Subsequently, we alternated 6MP with MTX on a weekly basis, in this way avoiding both MTX toxicity and 6MP resistance.

Besides antinuclear antibodies, lupus patients also develop anti-cytoplasmic antibodies. These serum factors react with cytoplasmic constituents from various organs. The reaction is not species-specific. The anticytoplasmic factors do not react with the intact cell and do not appear to be cytotoxic. In contrast to these organ non-specific anticytoplasmic factors, sera from patients with SLE often have an antibody-like activity against leukocytes which is specific for these cells. These anti-leukocytic autoantibodies also react against intact leukocytes and may contribute to the neutropenia often present in lupus patients (131).

Leukocyte-specific anticytoplasmic antibodies detected by immunofluorescence techniques gained practical importance upon the discovery of their association with small vessel vasculitides (ANCA: anti-neutrophil cytoplasmic antibodies). ANCA have become a useful diagnostic criterion, e.g. for Wegener's granulomatosis. These antibodies are probably the consequence and not the cause of the inflammatory vascular process.

Patients with hepatitis often exhibit a number of anticytoplasmic antibodies reacting with various cytoplasmic constituents (mitochondria, lysosomes, microsomes). These reactions are without organ or species specificity (125,128). No pathogenic activity of these serum factors could be detected; they do not penetrate living cells. A possible physiogenic function of antilysosomal antibodies has to be considered.

With the description of "lupus hepatitis", subsequently called chronic active or "autoimmune" hepatitis (145), we intensified our investigations on liver-specific antigens. In collaboration with K.H. Meyer zum Buschenfelde, we finally detected a liver-specific antigen, a liverspecific protein located within the cytoplasm, and a liver-specific lipoprotein located in the membrane of liver cells (189). Immunization of rabbits with a human preparation containing both antigens led in all animals to lesions characteristic of an immune hepatitis: infiltration with lymphocytes and plasma cells within the portal space, penetrating at different sites into the liver parenchyma, with piecemeal necrosis (202).

Today, we know that chronic active hepatitis (CAH) is in most cases associated with (and probably triggered by) the HC virus. In patients with HCV-associated CAH, we attempt first to eliminate the HCV with pegylated alfa-interferon (alfa-IFN) + Ribavirin. Unfortunately, alfa-IFN increases the inflammatory liver process and may thus aggravate the CAH. In this case, an alternative approach must be tried. Since immunosuppressive therapy leads to an increased proliferation of the HCV, we add Ribavirin and amantadan to the immunosuppressive regimen, which allows us to control the CAH without concomitant proliferation of the HCV.

Platelets were previously considered to be elements with immunologic specificity and always contaminated with fibrinogen. In collaboration with Fred Gorstein, we investigated the antigenic composition of platelets. These studies led to the detection of a platelet phospholipid. This constituent is not unique to platelets but is also present in red cells. It attracted increased attention with the discovery of the lupus anticoagulant, which turned out to be an anti-phospholipid antibody (110). Patients with such antibodies may be affected by one of the three clinical forms of the so-called antiphospholipid syndrome: 1) deep vein thrombosis; 2) cerebral thrombosis; 3) small superficial vein thrombosis. While this antibody is probably the consequence rather than the cause of

the vascular disorders, it interferes with pregnancy, leading to abortion if preventive treatment is not given.

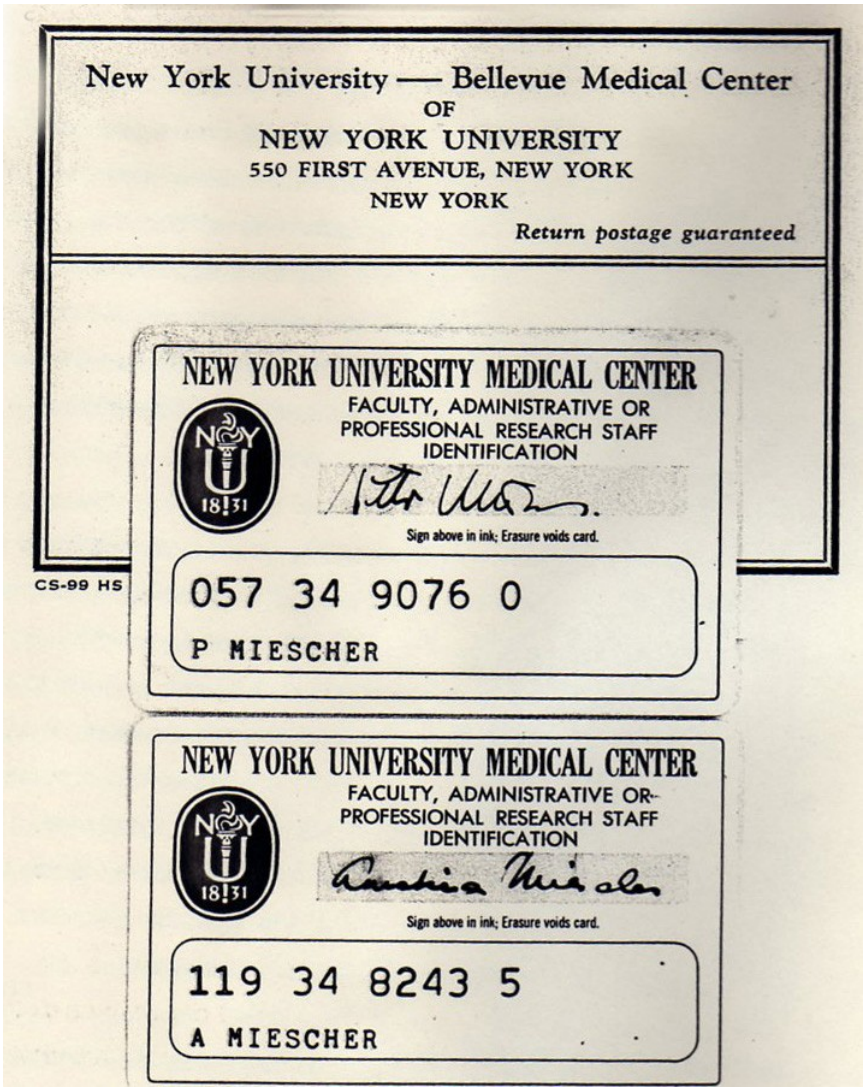
A few studies dealt with the phenomenon of immunologic tolerance. In a first series, we tried to induce tolerance to human erythrocytes in rabbits. The injection of large numbers of human red cells into newborn rabbits did not produce tolerance, but changed the anamnestic antibody response from 7S in control animals to a constant 19S response (129). The injection of the simple chemical compound dinitrophenylsulfonic acid (DNPS) into newborn guinea pigs prevented delayed-type hypersensitivity without suppressing antibody formation to DNPS (144). The induction of immunologic tolerance is a subject which is still under investigation in various laboratories searching for an antigen-specific treatment of autoimmune diseases.

One subject which we started to attack during my last year at NYU (1967) was the spleen. As a clinician, I was struck by the variation in spleen size in patients with collagen diseases. Indeed, one of the first signs of disease activity was the finding of a slightly enlarged spleen, sometimes tender on deep percussion, but not detectable by standard echography. In collaboration with Dr I. de Carvalho, our studies confirmed the role of the spleen in intravenously immunized rats. In particular, the presence of the spleen was shown to be important in the early 7S immune response (154).

Today, one of the practical clinical problems concerning the spleen is the exact assessment of its size. The introduction of echography with a conventional probe (centrifugal emission of rays) has led to the illusion that we have an accurate method of measuring the spleen. In fact, the results obtained by this method are very inaccurate, since the apparent spleen size on the screen varies with the distance between the source of the ultrasonic waves and the spleen. In search of a suitable method, I consulted various radiologists. Walter Bessler, an old friend and professor emeritus of radiology, discussed this problem with his successor and suggested that the linear echographic probe would be suitable for our purpose. Following his advice, we now use a linear probe which emits parallel beam waves, so that the size of an object does not vary with the distance between it and the source of the rays. Indeed, it has finally been objectified that an enlarged spleen is a major indicator of disease activity in most collagen diseases (272).

During the New York period, I was connected with an increasing number of institutions. The first and most important contact was with the National Institutes of Health (NIH). Being involved in the training of young research fellows, I was asked to join the panel of experts for the evaluation of grant applications. Three times per year the panel met at the NIH in Bethesda (Washington), on each occasion evaluating some 20 grant applications.

Robert Hickey, professor of surgery and executive director of the MD Anderson Institute and Tumor Clinic in Houston, Texas, became a close friend. We were both quick to assess the quality of candidates and usually both came to the same conclusion. Through him, I made the acquaintance of Lee Clark, president of the "MD Anderson", who asked me to become a consultant to his institute. My function as consultant was to discuss their respective research programmes with the various investigators of the MD Anderson; a most stimulating activity! I also became consultant to some of the pharmaceutical companies: Roche, for the evaluation of drug-induced side reactions; Merck Sharp & Dohme, to discuss new research projects; Syntex, to review ongoing studies with immunomodulating drugs (leflunomide was among the new compounds under investigation with promising



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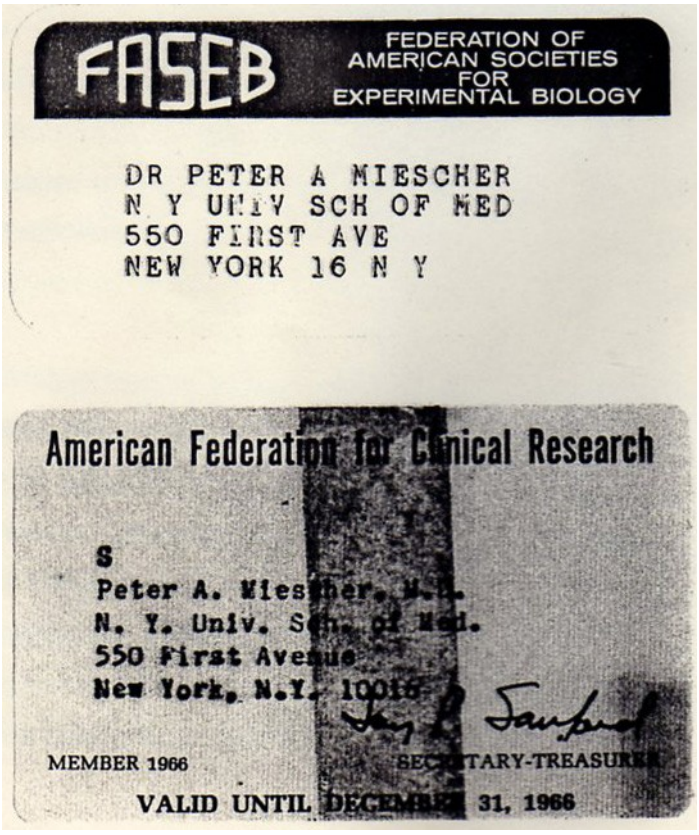

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MEMBER 1966

SECRETARY-TREASURER

VALID UNTIL DECEMBER 31, 1966

results, and finally introduced for the treatment of rheumatoid arthritis 5 years ago); the Ames Company, for the development of diagnostic procedures.

In 1960, I introduced at the NYU a new program of seminars in hematology with the aim of informing the house staff of recent developments in hematological research via presentations by leading investigators in the field. In 1962, Henry Stratton, president of the Grune & Stratton publishing house, having heard about these seminars, came to NYU to see me. Impressed by the quality of the presentations at these weekly seminars, he asked me if I would be prepared to publish them in a new type of journal, under the title "Seminars in Hematology". Henry Stratton was always in close touch with developments in Hematology. He had previously started the journal Blood, which became the leading hematology journal in the USA, and was one of the founders of the American Society of Hematology. I accepted, and this new journal, with 4 topical issues per year, soon had a wide distribution with close to 5,000 subscribers. After 40 years as founding chief editor, I passed this post on to Photis Beris, who was my best pupil in hematology in Geneva and who is well known in the international hematological community.

In 1963, I joined the American-Swiss Society. On the occasion of a visit to the society by Victor Umbricht, president of the Ciba company, we discussed research conditions in Switzerland which, compared to the USA, were lagging behind. Victor Umbricht suggested setting up a new society whose function would be to help Swiss universities keep abreast of developments in science and research in the USA. The members of the American-Swiss Society welcomed the proposal and the new society came into being. It was called the Swiss Society of Sciences (SSS) and I was elected as its president. The mandate given to the SSS was to promote contacts between Swiss and American academic institutions. One of the first projects was a meeting with federal counselor, Peter Tschudi, at the Bundeshaus in Berne to discuss coordination of research activities among the various Swiss institutions. Indeed, with the "unlimited possibilities, but limited financial means", it had become necessary to establish priorities and avoid dispersion of efforts. Following a constructive discussion, the SSS proposed to organize visits to selected USA universities by Swiss professors and university administrators. This proposal was received with enthusiasm and later realized thanks to a generous grant from Mr Max Kade, whom I knew as a patient.

Mr Kade had set up a foundation for the development of higher education in his home country, Germany, and kindly extended it to Switzerland. This grant made it possible to organize study tours for some 20 Swiss personalities, all involved in the management of academic institutions, to see first-hand the organization of medical schools and other academic institutions in the USA. The SSS organized these 2-3 week study tours individually, with visits to USA institutions chosen by the person making the tour. At the end of this project, we organized a symposium on "The Modern University" which took place in Geneva in the fall of 1968, with the participation of federal counselors Tschudi and Schaffner (at that time in charge of the economy). Amongst others, leading personalities from the USA such as Clark Kerr from California (at that time director of the Carnegie Commission on Higher Education), Alexander Bearn, chairman of the Department of Medicine at Cornell University, Lew Thomas, president of the Sloan Kettering Institute, came to Geneva for this symposium. I gave a talk on "coordination of research" (175). Carlo Henze, president of the Sandoz Foundation in the USA, played a very active role in this project as vice president and, after I left New York, as president of the SSS.

In the early years in New York, I had regular meetings with Hans Mueller-Eberhard, associate professor at

Rockefeller University. In 1966, we decided to edit a textbook of immunopathology as my earlier book in German written with K.O. Vorlaender had become out of date. The new book was a great success and after only two years we had to prepare a second edition. However, the field of immunology was expanding so rapidly that the speed of progress changed from a linear to an exponential development, impossible to follow with a third edition! At the time of the first International Symposium on Immunology held in 1958, there were about 30-40 scientists actively participating in the study of the then new field of immunology. But again, expansion was exponential, bringing the number of investigators to hundreds within the next few years, to thousands in the 1970's. Instead of a third edition of the textbook, we decided to create the journal "Seminars in Immunopathology" (now "Springer Seminars in Immunopathology") with the aim of informing physicians and pathologists about recent advances in this field by means of review articles prepared by scientists actively engaged in the respective fields. The first issue appeared in the spring of 1978.

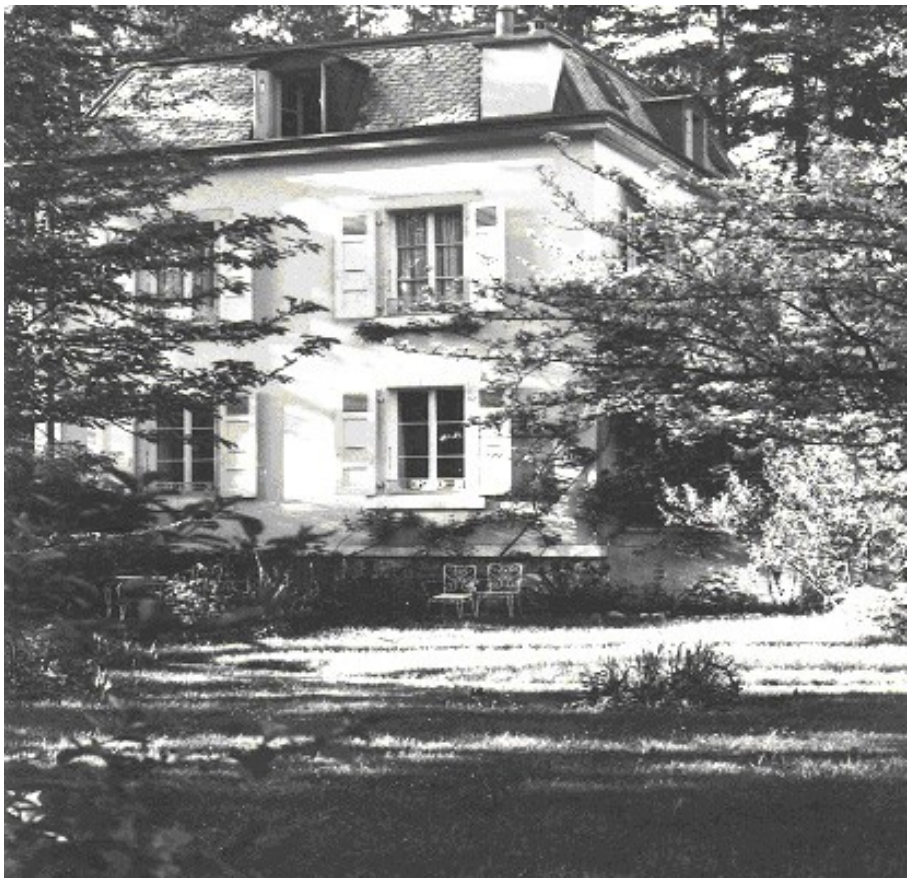
My connection with the World Health Organization also started in New York in 1963 when I was asked to join the WHO advisory panel in the field of clinical immunology. At the first meeting of the panel in Geneva in 1964, Dr Candau, director-general of WHO at that time, asked me to discuss the development of this important field. He had appointed Dr Howard Goodman as director of the WHO immunology program. The bridge to our "Geneva future" was thus established through WHO! Howard Goodman assessed the importance of immunological questions which would soon be of global interest. At that time (1967-68), there were still few centers in the world working in this direction, either for research or clinically. Goodman enlisted the collaboration of leading scientists in this field such as Baruj Benacerraf at NYU and Frank Dixon in Pittsburg (later at the Scripps Institute in La Jolla, CA), both close friends of mine since the old days of Lausanne and Basle.

5.1 Transition New York – Geneva

In 1966, I took a "sabbatical leave" and went as visiting professor to the Middlesex Hospital in London to work with Deborah Doniach and Ivan Roitt, both pioneers in the field of immunopathology of the thyroid gland. Dr H. Flad, one of our research fellows at NYU, joined me in London. He worked with Dr Playfair from the Middlesex Hospital on autoantibodies against liver antigens upon intoxication of mice with carbon tetrachloride (CCI4) as an example of autoantibody production upon tissue damage (173). During our stay in London, I gave lectures at the Middlesex Hospital and the Hammersmith Hospital. Annatina spent several days with the group of Professor Sir John Dacie to exchange experiences concerning diagnostic laboratory procedures. Professor Dacie was very interested in my work on immune complex (IC)-induced thrombocytopenia.

While we were in London, negotiations were in progress regarding my nomination for the position of professor of medicine in charge of hematology and director of the blood bank at Geneva University Hospital. At this time, Mrs Annette Kade, Max Kade's widow (he had died at the age of 84), informed us that her late husband had bequeathed funds to finance the appointment of a senior research associate. With the prospect of a transfer to Geneva, Mrs Kade suggested that we discuss this offer of funds with Dr Candau and her lawyer. The encounter took place in Geneva in spring, 1967, after my appointment to Geneva University Hospital had been finalized. Dr Candau was enthusiastic about this generous offer. We decided that the recipient of the "Annette Kade" WHO position should be in charge of a special WHO research unit within the university hospital. The successful candidate for this position would be chosen by me and Dr Howard Goodman as WHO representative.

GENEVA, Switzerland,1968-1994



PANORAMA DE L'HOPITAL CANTONAL UNIVERSITAIRE DE GENEVE

I immediately started negotiations with Geneva University and arrived at an agreement to create a WHO unit within the division of hematology. This made it necessary to prepare the infrastructure of the new hematology division to include the WHO unit. Furthermore, the dean of the NYU School of Medicine agreed to transfer CHF 100,000 (from the funds I had raised at NYU) for the construction of research laboratories. In Geneva, Mr Marcel Haas, director general of the hospital, obtained government permission to completely renovate the fifth floor of the policlinic building for the new activities. Thus, my first task in Geneva was to design with the architect the new division of hematology, including an air-conditioned meeting room for up to 35 people.

6. Geneva

In the summer of 1968, as "professeur ordinaire de médecine", I began setting up my professional headquarters at the Geneva University Hospital. My responsibilities included clinical hematology, the Geneva blood transfusion center, my newly-designed central laboratories of hematology and transfusional serology, the teaching of clinical and diagnostic hematology as well as clinical pathology.

I paid special attention to the building of adequate research facilities. I decided to integrate most research activities into the new WHO unit in order to coordinate all the programs of the various young associates.

One of the first priorities was to find a suitable candidate for the new WHO research post. We chose Francis Jeunet, a young Swiss research fellow well trained by Robert A. Good in Minneapolis, Minnesota (Good was a pioneer in the field of agammaglobulinemia and a codiscoverer of the role of the thymus). After a year, Jeunet was offered, and accepted, a position at Hoffmann-La Roche in Basle. So, Howard Goodman and I looked for a replacement and selected Paul-Henri Lambert from Belgium. Dr Lambert had been a pupil of Frank Dixon and under him had already worked on subjects involving immune complexes (a research field we shared with Dr Dixon).

6.1 Scientific activities

The first study, dealing with the detection of IC in patient's serum with different concentrations of polyethylene glycol (PEG), was carried out with a young research fellow from the USA, W.D. Creighton (214). Based on this study, Nydegger and Lambert developed a radioimmunoassay with coprecipitation of I-125 labelled C1q (component of complement) in the appropriate concentration of PEG. This study led to the C1q fixation test, which rapidly became the standard method for detecting circulating IC (215).

With the increasing interest in the diagnosis of hepatitis B carriers, Lambert developed a radioimmunoassay with I-125 labelled Fab anti-HbAgS, again making use of PEG for coprecipitation (217). This method permits to detect HbAgS even in the presence of excess anti-HbAgS. At that time, immunoglobulin (IgG), prepared from the serum of persons with a positive test for these anti-HB antibodies, was used for the prevention of hepatitis B in exposed subjects. At one industrial plant in Brazil, a German preparation of IgG antiHBAgS, apparently free of AgS, was used for this purpose. Since a few people from the plant developed hepatitis B following this prophylactic treatment, WHO was asked to investigate the situation. Dr Candau was pleased to be able to call upon our newly founded WHO research unit. The "questionable anti-HBAgS preparation" was analyzed in our WHO unit. The newly developed radioimmunoassay gave a positive result for the presence of HBAgS in this commercial "anti-HBAgS gammaglobulin" (embarrassing for the pharmaceutical company!).

Still in the field of IC, Nydegger demonstrated a stimulation of the polymorphonuclear leukocyte activity (increase of the hexose monophosphate shunt) by insoluble IC (211). Finally, circulating as well as intra-articular IC were demonstrated in patients with active RA (252) as well as in the peripheral blood of patients with SLE and in carriers of HBV (226).

With the group of Nydegger and Perrin, we also studied complement and properdin degradation products to assess their participation in immunopathologic processes. Indeed, in the joint fluid of patients with RA we not only find IC, but also breakdown products of complement and properdin (238). Similar findings were obtained in the plasma of SLE patients as well as in the plasma of patients with hypocomplementemic glomerulonephritis (242).

You-peng Huang attacked the difficult subject of the role of Th cells in the pathogenesis of SLE. Th cells activate B cells via the interleukin, IL-2. Huang found a decreased IL-2 secretion by Th cells in lupus patients, which became normal after these cells had rested for a few days in culture. Conversely, IL-2 serum levels were increased in 9 out of 18 patients with active disease, indicating that Th cells have been active in the production of IL-2, ending up with a diminished capacity to secrete additional IL-2. In cell culture experiments, IgG secretion by purified B cells from 6 out of 9 patients with active SLE was increased when stimulated by autologous Th cells. These experiments provided evidence that increased T cell activation occurs and plays a role in the pathogenesis of SLE (274).

The following case illustrates the action of IL-2 on B cell activity., resulting eventually in hypergammaglobulinemia. In a patient I was treating for chronic lymphocytic B cell leukemia (B-CLL), a polyclonal hypergammaglobulinemia appeared with 38.3 g/L of IgG. This finding was surprising, since patients with B-CLL regularly develop a decrease of gammaglobulin production. In vitro studies with the leukemic B cells

of this patient showed an extraordinarily high production of IL-2. The polyclonal IgG seen in this case of B-CLL must have been produced by normal B cells which had been stimulated by IL-2 produced by proliferating monoclonal (leukemic) B cells (276). Interestingly, this patient responded favorably to treatment with cyclosporin A (diminution of IL-2 production).

Amongst my last cases in New York, Maryline Schittoni, one of our attending hematologists, presented to me a few patients with a condition characterized by monocytes of abnormal appearance in the peripheral blood and with a bone marrow rich in myelocytic-like cells. The other cellular constituents of the bone marrow showed "dystrophic" transformations and a diminished number of megakaryocytes, mostly small forms. One of my first patients in Geneva presented the same condition which I called "myelomonocytic leukemia" (MML). Subsequently, we diagnosed MML in an increasing number of patients, all of an advanced age, with a slow evolution of their disease and frequently showing a moderate to severe thrombocytopenia, mild anemia and a late appearance of hepatomegaly and lymphadenopathy. The serum lysozyme level in MML is increased. I showed slides of these patients to John Dacie, our first visiting professor in Geneva. He agreed that we were dealing with a new syndrome, which he actually had also observed in London without having thought to publish it. I asked one of our clinical fellows, Jerome Farquet, to publish our Geneva patients (220). These cases led us to investigate the myelodysplastic syndrome, which is characterized by a number of morphologic criteria representing monoclonal conditions. (In fact, Dacie was the first to describe a "double red cell population" in patients with sideroblastic anemia, concluding that this was due to a monoclonal proliferation of mutated precursor cells). In the meantime, other hematology centers started to investigate the following three types of myelodysplastic syndrome (MDS): primary refractory anemia, sideroblastic anemia and MML. In all these conditions, chromosomal abnormalities were found, some even permitting to differentiate between clinical forms of the MDS, all with the potential to eventually develop into acute leukemia (282).

In contrast to this group of MDS with signs of monoclonality, I followed a few patients (ending up with 11) who all showed signs of myelodysplasia without signs of monoclonality. These patients had erythroid series with megaloblastoid features and signs of dyserythropoiesis, myeloid series with shift to more immature forms, and a diminished number of megakaryocytes resulting in thrombocytopenia. The mature neutrophilic leukocytes were normally granulated, without the Pelger abnormality (in contrast to degranulated leukocytes in refractory anemia). The kayotype was normal in all 11 cases. Furthermore, no patient from this group developed leukemia, and all responded well to immunosuppressive treatment including cyclosporine (273). It is interesting to note that, under immunosuppressive therapy, patients with aplastic anemia develop a condition similar to autoimmune myelodysplasia. Today's concept of aplastic anemia postulates a somatic mutation of the hematological stem cell with a secondary "autoimmune" response against the new clone. We postulate a similar mechanism for the pathogenesis of autoimmune myelodysplasia. As a matter of fact, transitions exist between aplastic anemia and autoimmune myelodysplasia.

In our experimental work with mice, we introduced into our animal quarters a colony of NZW (resembling SLE) mice, and NZB mice, for which we had no human equivalent at that time. With the nephrologist, Professor Hervé Favre, we followed 4 patients who provided the missing link: these patients presented signs of hemolytic anemia and/or thrombocytopenia. Furthermore, they developed at some stage of their disease antinuclear antibodies and circulating IC. Renal biopsy revealed granular deposits of IgG, IgM, and complement. Upon optic microscopy, 3 patients had mild mesangial proliferation, one patient a focal glomerulonephritis. Upon electron

microscopy, all 4 patients exhibited mesangial and/or subendothelial deposits. During the follow-up of 18 to 37 years since the onset of their disease, no patient developed clinical evidence of SLE. These patients thus have a clinical syndrome equivalent to that of the black NZB mice which present immunohematological disorders and some biological markers of SLE without developing a full clinical picture of SLE. These 4 patients probably have a genetic background similar to that of NZB mice, but different from that of SLE patients (263).

The main motivation for my research activity came from patients suffering from immunopathological disorders. As a matter of fact, I always wanted to understand the underlying immunopathological process in order to develop a treatment regimen based on mechanisms of disease. The first part of my academic life was devoted to the study of immunopathological events leading to disease, the later part to the development of treatment regimens, taking advantage of the progress made in the field of immunology and in the development of new immunomodulating drugs.

Whilst in Lausanne I had already realized the dangers of cortisone. I tried an association of cortisone with antimalarials, initially with atebrin, subsequently with chloroquine. This latter compound proved efficient in cutaneous vasculitis mediated by delayed type (cellular) hypersensitivity (60). Today chloroquine has been replaced by hydroxychloroquine, which is less toxic for the retina. In 1958, Schwartz introduced the antimetabolite, 6-MP, which was successfully used as a cortisone-sparing immunomodulating drug. In 1963, we studied the antimetabolites 6-MP and methotrexate in experimental autoimmune thyroiditis, a condition due essentially to cellular immunity. Both drugs proved effective in preventing as well as treating already-established thyroiditis (121). In 1964, Burroughs-Wellcome offered a modified 6-MP, azathioprine, a 6-MP molecule to which an imidazole ring had been attached. The slow release of 6-MP in the liver was thought to represent an advantage. In my experience, the two compounds are equivalent. Some patients tolerate azathioprine better, others 6-MP (133).

In 1970, the alkylating agent, cyclophosphamide (Cy) was introduced for the treatment of RA by Alepa et al, initially in an oral administration of 100 mg/day. At the beginning, we also used Cy orally, without relevant side effects in a case of interstitial pneumopathy (229). Subsequently, we compared Cy at the dose of 100 mg/day with 6-mP (50 mg/day) in lupus patients. Cy produced more side reactions (nausea, alopecia). After the occurrence of leukemia in 1979 and 1980 in two of our patients on long-term oral Cy, we ceased oral administration of this drug. Thereafter we used Cy only in the form of i.v. pulse-therapy. It should be added that Cy pulse therapy is probably one of the most efficient means of producing immunosuppression, always bearing in mind its potential cancerogenicity and its toxic effect on the ovaries. Fortunately, out of more than 400 patients on i.v. pulse therapy, not one has developed leukemia or any other type of malignancy during the past 25 years (272).

Since all available immunosuppressive drugs have a dose-dependent toxicity (steroids, 6MP, methotrexate, Cy, hydroxychloroquine, cyclosporine, as well as the more recent biological compounds), drug combination therapy appeared to be the logical solution to the problem of how to adjust treatment intensity to disease activity with a minimum of side reactions (272).

With regard to steroids, even given at low doses, the question remains of how to eliminate cortisone dependency. In a first trial, we introduced one steroid-free day per week (209,229). In 1985, we studied

adrenocortical responsiveness after discontinuous corticosteroid therapy (264). The results of this investigation determined our present steroid medication schedule. One steroid-free day per week is insufficient to maintain a satisfactory adrenocortical responsiveness. With two non-consecutive steroid-free days per week, we only lose about 10% of the responsiveness of the adrenal gland to the action of ACTH, provided we use a steroid with a short biological half-life (prednisone, fluocortolone, cloprednol and, to a lesser extent, methylprednisone). The two steroid-free days permit the organism to react promptly to infections, or to undergo surgery without complications.

Plasmapheresis was successfully introduced for certain antibody-mediated conditions such as myasthenia gravis, immune hemolytic anemia and certain forms of vasculitis. Plasmapheresis alone provides short-term benefit. If followed by a Cy-pulse, the effect is prolonged because of the suppression of antibody production by Cy. In certain conditions, high-dose, i.v. gammaglobulin has also been shown to increase the efficacy of plasmapheresis. I introduced plasmapheresis (on an out-patient basis) in Geneva in 1979 with Urs Nydegger and Christina Egg. Christina Egg became an expert with this procedure, which is not without risk for patients with cardiovascular disorders (281).

In 1982, Dr Beat de Graffenried from Sandoz proposed that we conduct an open trial with Cyclosporin A (CsA) for SLE patients not responding well to the drug combination of low steroids + MTX + azathioprine. In the Sandoz protocol, the initial dose was 10 mg/kg/day in 2 doses per day. Fortunately, the mother of the first patient, a 10 year-old girl with SLE, called me after 2 days to inform me that her daughter did not tolerate the drug. I lowered the CsA dose to 7.5 mg, which was still not tolerated. Finally, at 5 mg/kg/day, the girl tolerated CsA well and this became our standard dose for all patients.

In 1983, the first alarming reports appeared about the nephrotoxicity of CsA at a dose of 10 mg/kg/day. Dr De Graffenried and Dr. William Harrison, with whom I had a most productive and enjoyable collaboration, were relieved that I had used CsA at only half the recommended dose. They agreed to my suggestion to perform a kidney biopsy in all our patients on long-term CsA medication (usually after 2 years, with a second biopsy after 5 years of CsA medication. The results of this study were encouraging. Only minimal changes were seen in some biopsies (279). In subsequent years, Professor Favre did 192 kidney biopsies in our patients on long-term CsA medication, which showed no or only insignificant signs of CsA toxicity (269, 271, 278). Furthermore, long-term medication (15 to 23 years) did not lead to impairment of kidney function (272).

Amongst the first patients under CsA medication, 4 patients suffered from a very severe form of RA. During the first 2 months, we limited the treatment to the steroid-CsA combination but the effect was considered too weak for 3 of the 4 patients. When we added MTX, 15 mg i.m. per week, 3 weeks out of 4, the therapeutic effect became much more obvious both to the patient and according to objective evaluation (279).

In 1988, we published a detailed study of 9 patients suffering from a severe form of RA. The combination of CsA, MTX and steroids had proved very effective as measured by a clinical and biological score. The biological score was based on in vitro cell culture tests: 1) the capacity of T cells to produce IL-2, and 2) the amount of IgG spontaneously produced by B cells within a 9-day culture period (277). In this study, we stressed once more the importance of early intervention, before the occurrence of irreparable damage, and in order to avoid the clonal expansion of T and B cells in an ongoing immune response (resulting in escalation of the disease process).

In 1986, I published our experience concerning the treatment of SLE in 41 patients (265). For such long-lasting diseases with unpredictable evolution (depending on genetic and very much also on environmental factors), it is important to establish a long-term treatment strategy. CsA has become a very efficient basic drug for combination therapy of SLE, despite the fact that SLE affects the kidneys in most patients (278). Creatinine-monitoring has become the most pertinent test for assessing renal toxicity of CsA. Only patients with a creatinine level under 1.4 mg/dl should receive CsA. We also learned that abrupt discontinuation of CsA may produce a rebound of disease activity. Patients were warned of this complication. Since SLE is a predominantly Th-2-mediated disease, steroid pulses have shown to be very effective in treating acute exacerbations of the disease (269).

In this study (265), I mention our experience with intrathecal treatment of cerebral lupus and multiple sclerosis. Intrathecal treatment has proved successful, provided it is given promptly in the event of an acute exacerbation. Additional cases of cerebral lupus have been published in collaboration with the Brescia group and the group from the Umberto-Primo Medical Center, La Sapienza University, Rome (268).

In 1994, we published the long-term results of drug-combination therapy in 246 patients with SLE (269). 124 patients were well controlled with steroids plus antimetabolites (MTX, Aza); in 46 patients it was possible to discontinue CsA (tapered gradually) after 4 to 6 months; 3 patients did not tolerate CsA. The remaining 73 patients were under CsA medication during the entire observation period (7.1±1.91 years); in 19 patients combination with steroids was sufficient to control disease activity; in 24 patients MTX had to be added; in 30 patients who had the most severe expression of SLE, a quadruple combination therapy with steroids/CsA/MTX/Cy was necessary to control disease activity. This long-term study on 73 patients with severe SLE showed that drug combination therapy with steroids, CsA, MTX and Cy permits control of disease activity, maintenance of kidney function with very few side effects and, to a large extent, allows patients a good quality of life in both professional and personal terms.

In 1998, we reported on drug combination therapy in 82 patients (271) suffering from a severe form of RA. This study permits the following conclusions:

1) Drug combination therapy with a medication regime adjusted to the changing disease activity is well tolerated and causes minimal toxicity (in no patient was it necessary to discontinue treatment).
2) Early immune intervention appears essential to obtain good results.
3) Patients with irreparable joint damage still respond to drug combination therapy, but to a lesser degree and with a high tendency towards relapse when encountering trigger factors such as intercurrent infections.
4) With doses of CsA below 5 mg/kg of lean body weight, this drug can be given for prolonged periods of time without the danger of relevant kidney damage. Monitoring of creatinine values is mandatory.
5) Side reactions were mild, compatible with continuation of therapy. In particular, the liver parameters remained in the physiologic range, as did the creatinine levels. The 51 kidney biopsies carried out revealed minimal signs of toxicity attributable to CsA medication (striped fibrosis, CsA-associated arteriolopathy) in 14.6% of the patients.

In patients with chronic autoimmune diseases, where activity is variable depending on genetic, environmental and disease trigger factors, accurate monitoring of disease activity is mandatory. Indeed, treatment has to be constantly adjusted to the disease activity.

6.2 The role of the spleen in the evaluation of disease activity

The assessment of disease activity requires both clinical and laboratory parameters. For most of the collagen diseases, variations of the splenic dimensions are the most reliable clinical signs of disease activity. The following autoimmune conditions cause an enlargement of the spleen when the disease is in an active phase: juvenile idiopathic arthritis, Still's disease, idiopathic uveitis, dermatomyositis, polymyalgia rheumatica, primary Sjogren's syndrome, progressive systemic sclerosis, Wegener's granulomatosis, ChurgStrauss syndrome, Crohn's disease, ulcerative colitis, ankylosing spondylarthritis, chronic active hepatitis, primary biliary cirrhosis, recurrent-intermittent pericarditis, interstitial pneumopathy, peripheral autoimmune motor neuropathy, Behcet's syndrome, sarcoidosis, Cogan's syndrome, also without ocular involvement, hypocomplementemic glomerulonephritis and lichen ruber planus. The spleen can also participate in severe forms of Basedow's disease, myasthenia gravis and IgA nephropathy with skin involvement.

The spleen is not involved in MS, mild forms of discoid LE, mild forms of psoriasis, pemphigus, and bullous pemphigoid.

The variations in the splenic dimensions in these autoimmune diseases are below the threshold of conventional echography of the spleen. However, they can be accurately measured by linear echography with the use of a "linear probe". With the importance of the spleen in the assessment of disease activity in these autoimmune conditions, this new technique should become the standard method for clinical evaluation.

Why is the spleen involved in some, but not all, autoimmune diseases? We know that i.v. immunization of rats requires the spleen in order to produce a full immune response (154). With regard to autoimmune diseases in humans, we have to postulate that in those conditions in which the autoantigen passes into the circulation, the spleen becomes the appropriate organ to produce an "autoimmune response". Indeed, the conditions within the spleen are all fulfilled: presence of antigen-presenting cells, B and T lymphocytes, and the slow passage of the autoantigen through the white pulp.

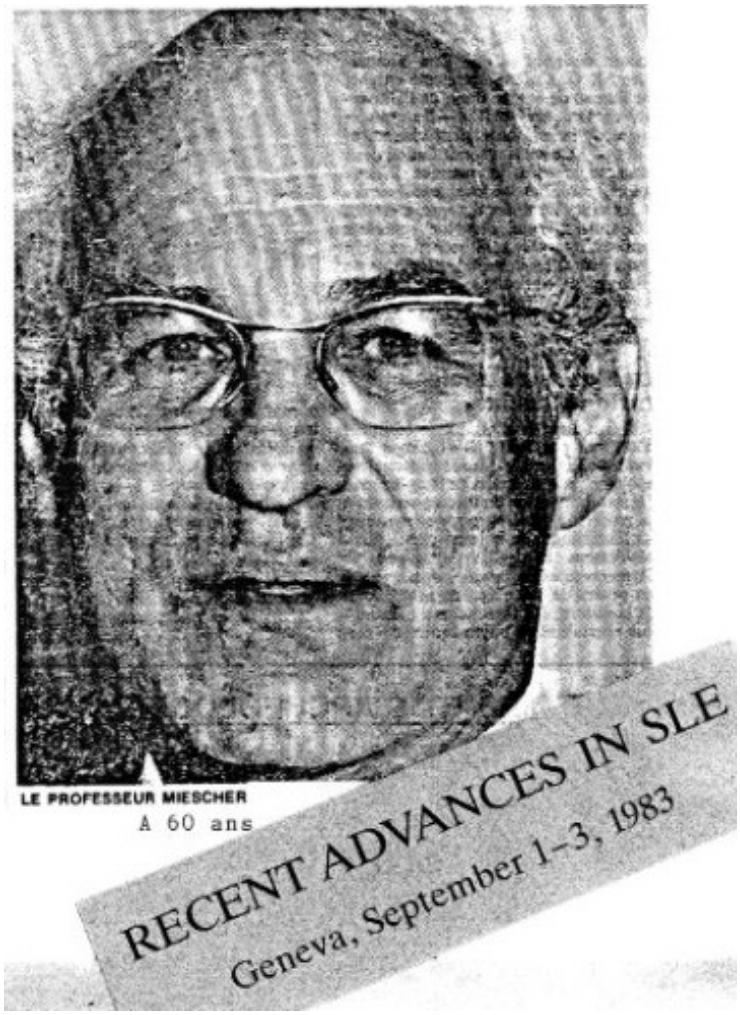
The following example of activation of disease in a case of RA illustrates the sequence of events, triggered by liberation of joint-specific antigen (RA-Ag) at the site of an alreadyaffected joint with a periarticular pannus. A simple trauma can lead to local liberation of RAAg, which in the pannus encounters antigen-presenting cells which engulf the antigen. The presentation to disease-specific T lymphocytes produces secretion of II-1 and TNF (tissue necrosis factor). The latter in particular produces an inflammatory reaction with liberation of additional RA-Ag, which then passes into the circulating blood and reaches the spleen. The RA-Ag encounter specific B lymphocytes, acting as antigen-presenting cells, and monocytes, which together produce an autoimmune response with specific T lymphocytes. This process leads to liberation of interleukins, including gamma-INF, IL-1 and TNF. This cellular interaction produces swelling of the spleen, which may actually become tender.

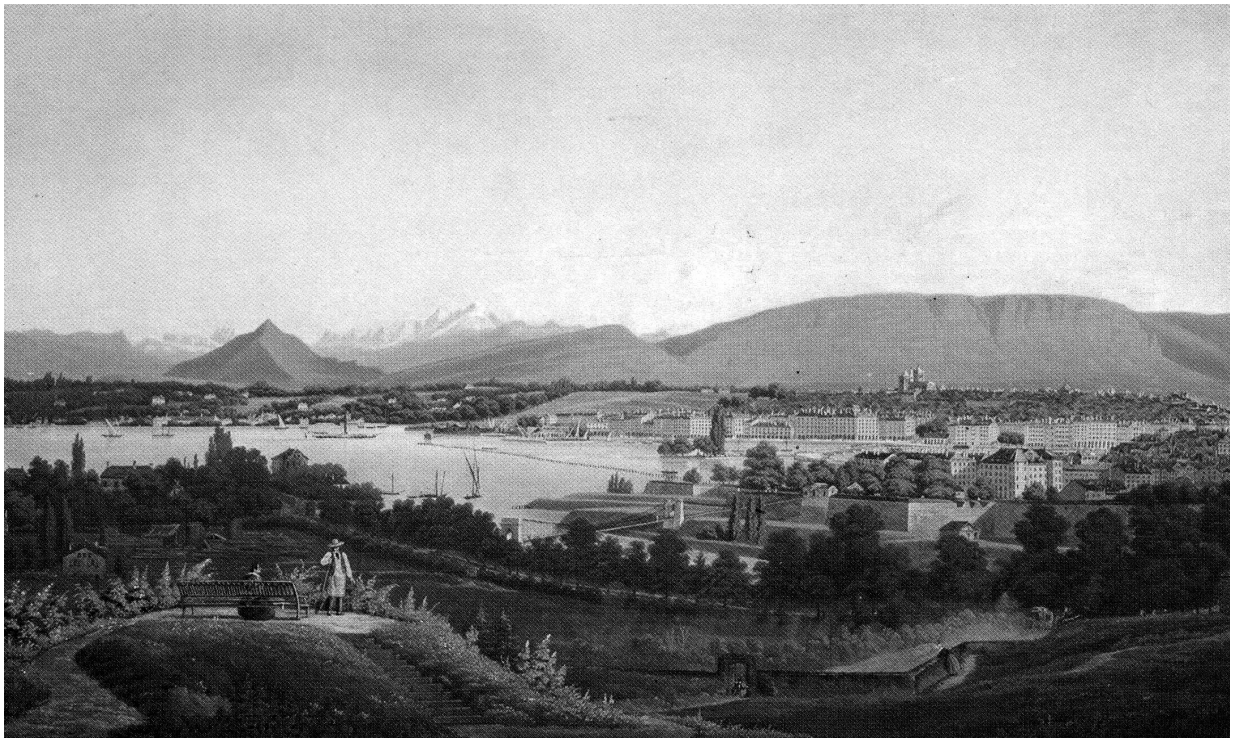
Clonal expansion of anti-RA-Ag B and T lymphocytes, which enter the circulation and increase disease manifestations in susceptible joints, maintain the vicious circle with additional liberation of RA-Ag. This complex mechanism of cellular interaction leading to disease can be attacked through medication at two levels: 1) by

immunosuppressive agents, acting on the cells engaged in the immune response (e.g. CsA, MTX); or 2) by biologicals neutralizing TNF, either directly (infliximab), or through the TNF receptor (etanercept). Today, the physician is inclined to use monotherapy with an anti-TNF agent which rapidly blocks the joint aggression, relieves the patient's pain, but does not affect the cellular part of the immune-aggression, i.e. the B and T lymphocytes as well as monocytes. In theory, antiTNF treatment may also slowly calm the immune response by reducing the amount of RAAg liberated, RA-Ag being the immune response triggering agent. Yet, we have observed patients under anti-TNF treatment relapsing upon encounter with disease-triggering events, with enlargement of the spleen. Thus, experience supports the theoretical conclusion that anti-TNF also has to be given in a drug-combination, for instance with CsA + MTX, which prevents B and T lymphocytes from reacting with monocytes.

This example stresses the need for flexibility in the treatment of patients with autoimmune diseases, but also the importance of the physician being readily available in order to rapidly adjust treatment in the event of an exacerbation of the disease process.

Nowadays we have the choice of over 20 immunosuppressive drugs which act on different sites of the afferent and efferent immune response, as well as on the migration of T and B cells from the circulation into the tissues involved in the various autoimmune diseases. Conditions today are such that it is possible to offer therapeutic drug combinations according to the mechanisms involved in the different autoimmune disorders (272).

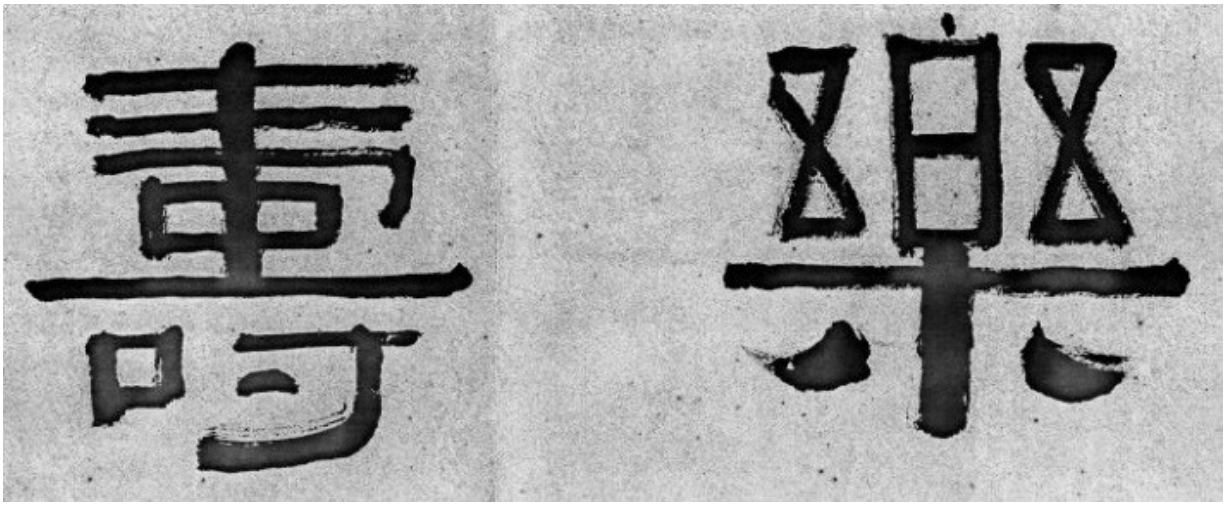




GENEVE ET LE MONT-BLANC

Professor CHANG An from Capital Hospital, Beijing

Our first friend in China, professor Chang An, wrote the following ideograms for Peter's 60th. Birthday!



"He who is benevolent, will attain old age"

"He who has wisdom, will enjoy happiness"

WORLD HEALTH ORGANIZATION

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Ref. : DDG

16 October 1978

Dear Professor Miescher,

Confirming our recent conversation, I have pleasure in inviting you to act as a Temporary Adviser from 12-19 November 1978 to assess the needs of the People's Republic of China in the area of biomedical research in general, and in basic medical sciences in particular; to ascertain where the deficiencies lie in collaboration with European institutions of biomedical research; and to assist in the rapid build of young scientists to bridge the gap.

It is understood that your travel expenses will be covered independently and Dr Ch'en has confirmed that the Government of the People's Republic of China has kindly offered to cover all your expenses within the country.

Baggage insurance will be taken out on your behalf by the Organization for the period of the assignment and personal accident insurance as shown on the attached form.

I should be grateful to receive your official acceptance of this assignment.

Yours sincerely,

V. Lambo

Dr T.A. Lambo
Deputy Director-General

Professor P.-A. Miescher
Médecin-Chef
Centre de Transfusion sanguine
Hôpital Cantonal
25 rue Micheli-du-Crest
1211 Geneva 4

6.2 WHO Research Unit Of The Geneva Blood Bank (1968 - 1983)

Since 1959, Peter Miescher was associated with the WHO immunology programme, first with Dr N. Jerne as head of the Immunology Unit, and subsequently with Dr H. Goodman, who became involved in the organization of the international symposia on immunopathology co-sponsored by WHO. Dr Candau, director general of WHO, always took a special interest in these activities. Each time Peter Miescher visited WHO he met with Dr Candau who wanted to discuss the developments in immunology relevant to WHO's programmes. When Peter Miescher was invited to join the Faculty of Medicine in Geneva, Mrs Annette Kade from New York offered to sponsor a new investigatorship within the Geneva Blood Bank. Peter Miescher discussed this offer with the Department of Public Health in Geneva (Mr Willy Donze) and with the hospital management (Mr Marcel Haas) as well as with Dr Goodman and, of course, Dr Candau. These negotiations led to an agreement to found a WHO Research Unit within the Blood Transfusion Centre of Geneva Hospital with the understanding that the holder of the new position would be in charge of co-ordinating all research activities carried out within Dr Miescher's group (financed by university funds, hospital funds, the Swiss National Foundation, private funds, and WHO). The agreement was finalized in April 1968 at a meeting at WHO between Dr Candau, Dr Goodman, Mrs Kade and Peter Miescher. At that time, WHO already had a similar unit within the Department of Biochemistry at the University of Lausanne (WHO Reference Laboratory). The first recipient of the Annette Kade investigatorship was Dr Francis Jeunet who held the position from September 1968 until the end of 1969 when he moved to Basle. Dr Goodman and Dr Miescher formed a search committee to find the best person to replace him. Dr Paul-Henri Lambert was selected and started his activities in January 1970.

In subsequent years, the WHO Research Unit proved successful. In addition to research activities, Dr Lambert organized the WHO training courses in immunopathology which had been initiated by Dr Goodman. When Dr David Rowe, at that time chief of the WHO Reference Laboratory in Lausanne, was promoted within WHO headquarters, it was decided to combine the two units under the designation "WHO Geneva-Lausanne Research and Training Centre", with Dr. Lambert as head of both units. Dr. Lambert's position became integrated within the WHO regular budget while the Annette Kade investigatorship was made available for the successor of Dr. Rowe, Dr. Jacques Louis.

When the Annette Kade Fund came to an end in 1976, the position was retained based on a guarantee of payment from the Hematology Fund of the WHO Research Unit, and by payments from the Belgian government and from Interpharma, Basle. In 1980, WHO decided to incorporate the Lausanne position also into its regular budget.

The establishment of the WHO Research and Training Centre was ratified in 1975 by the two Faculties of Medecine, following negotiations with the Faculty of Lausanne led by Dr Goodman and negotiations with the Faculty of Geneva led by Dr Miescher.

Today, the WHO Research and Training Centre can be considered as established in the service of medicine. With support from federal, cantonal, private and international funds, it has been possible to train investigators from Switzerland as well as from many parts of the world in this centre, and to further research in different sectors of hematology and immunology.

August, 1983.

7. "China Mission" (WHO) through the eyes of Annatina Miescher

7.1 First contacts with the Chinese Mission to the United Nations, Geneva

In 1976-77, a long time after the American President, Richard Nixon, made his famous visit to Mao Tse Tong in 1972, the first Geneva officials were allowed to visit China and Tibet. It was in 1976 that we were invited to the Chinese mission in Geneva to attend a dinner with the Chinese ambassador, An Chi Yuan. It was an unforgettable experience; An Chi Yuan repeatedly raised his glass (at very short intervals) with the exhortation "Down with the gang of four!". The "soirée" ended abruptly after a sip of Maotai (45° oechsle sorghum alcohol - as we learned later, the traditional after-dinner liqueur in the PRC in those days and the 20 years following). We realized that a new era had started and that in the near future the Middle Empire would open to the rest of the world.

In 1977, we were privileged to have to stay with us for one week in our mountain home in Ftan (1650 m altitude) Ambassador An Chi Yuan, his wife (who, apart from Chinese, spoke only Russian), his translator Chen Wen-to, Zao Ping (the "joy" leader of the group), his secretary, and his chauffeur from Shanghai. . Not many people at that time had seen a real live Chinese. They had chosen our home as a base from which to visit a provincial hospital and to see how it functioned. All went well; the hospital in Samedan was extraordinarily accommodating and let the visitors see all aspects of how the hospital was run: operating rooms, patient's quarters, sanitary installations, kitchens, etc.

The great wall in China, we saw in 1978 the first time

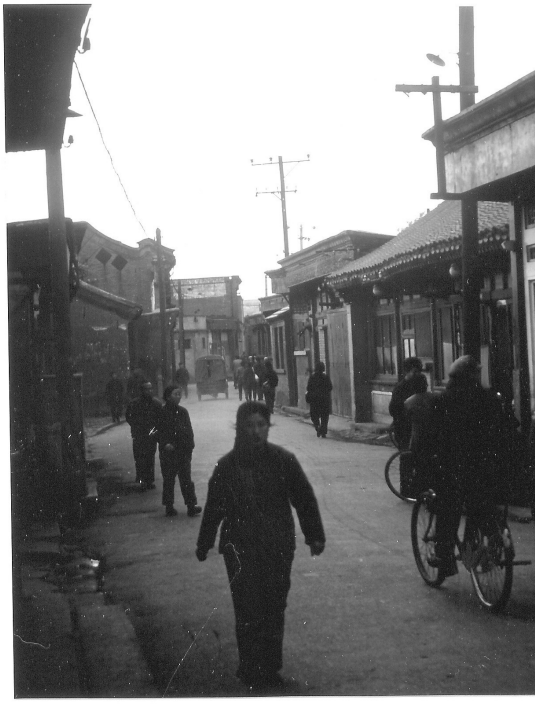
Our visitors then wanted to see the highest possible mountain peak in our eastern Alps. A trip to the Bernina (4,050 m) would have been difficult so we decided on the Ortler (3,900 m, in nearby Italy) which has a funicular railway going up to the vast glacier. So, keeping on our summer shoes and taking a little jacket with us, off we went to the lofty heights. It was a splendid day in July and we decided to show our guests more of the alpine paradise. Therefore, on the return journey, we took a different mountain pass: Umbrail instead of Stelvio). This was a big mistake since the Italian frontier guards at the Umbrail, above Munstertal, refused to let our two cars cross back into Switzerland, since our guest had a permit which allowed him to use just one frontier control post to leave and return to Switzerland. It was nine o'clock in the evening, everyone had cold feet and empty stomachs, and no bargaining seemed possible with the frontier guards. Finally, one of them said "Go!", adding that while they had ample time to admire our guests' passports, they could not understand anything. So, thanks to the ideograms and wonderful calligraphy which had overwhelmed the admirable guards, we were able to continue our journey!

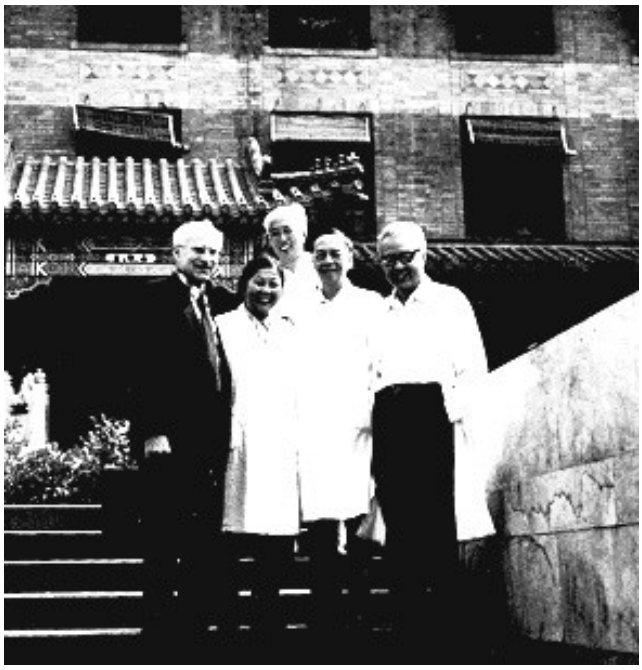
After this eventful opening with PAM acting as chauffeur of the huge embassy Mercedes limousine (explanation: the Shanghai chauffeur kept his foot on the brake all the time when going downhill, until clouds of dark smoke made him stop. Excuse: in Shanghai, all driving is on flat roads!) we had won the confidence of the mission and in November 1978, we were invited to visit China.

Preparations for our first trip to China took more than a year. Dr Candau, director general of WHO at that time, started negotiations with the PRC's Ministry of Health.

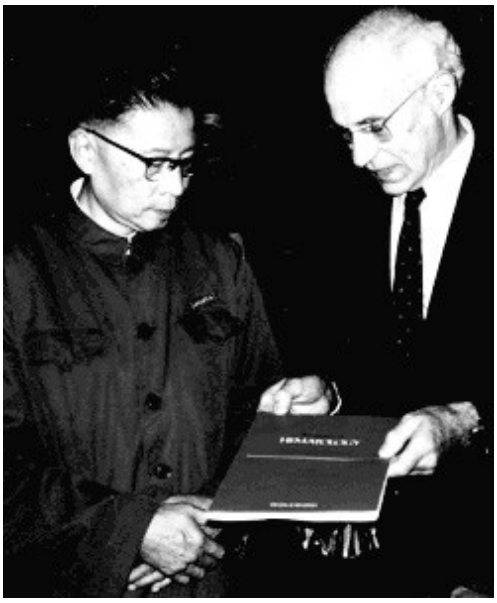
7.2 First visit to the Chinese Academy of Medical Sciences and two main hospitals in Beijing

1978: The purpose of the first trip to the PRC was to meet the leading physicians at the Capital Hospital in Beijing (Professors Chang An and Fang) and the staff in the Friendship Hospital, as well as to visit the Chinese Academy of Medical Sciences with the immunologist, Professor Wang (both institutions also situated in central Beijing). Our report on this study tour is reproduced below:



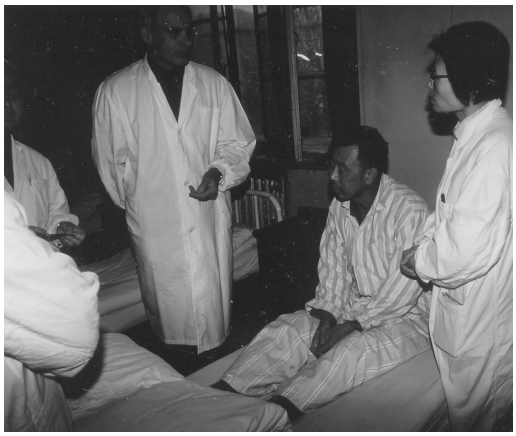


1978 BEIJING Capital Hospital



“Seminars in Hematology”

Friendship Hospital



Lupus treatment discussion

Oldest professor: STILL ACTIV

IN NOVEMBER 1978 on the GREAT WALL

…a few glimpses of a private China!

REPORT ON A MEDICAL STUDY TOUR MADE IN CHINA BETWEEN 13 AND 18 NOVEMBER 1978

1. Introduction

The purpose of this short study tour was to make a preliminary approach towards the assessment of the needs of the People's Republic of China in the area of biomedical research and health care and to formulate proposals as to how best assist the country in its future development within this sector of the modernization program.

To facilitate a better understanding of the present situation with regard to medical education, health care and biomedical research in China, we first give a brief survey of the evolution during the past 30 years.

We then report on our visit to the Institute of Basic Medicine of the Chinese Academy of Medical Sciences, from which we were able to gauge the level of biomedical research, and on subsequent visits to two hospitals (Capital Hospital and Friendship Hospital), all in Beijing, which permitted us to evaluate the quality of health care mainly in the field of hematology and immunology as applied in these two excellent establishments.

Finally, we have tried to formulate proposals as to the further development of biomedical sciences within the scope of the modernization program.

2. Biomedical research within the last 30 years

It is our understanding that modernization in the field of health sciences is based on biomedical research. Though the rich field of traditional medicine will keep its place in China, most innovations will have to come from research. Therefore, we shall assess the present situation by examining first what has happened in this respect during the last 30 years.

2.1 1949-1957

This phase was characterized by the influence of the USSR on the various developments within the country. Medical research reflects that trend with the main emphasis being placed on the central nervous system, following the school of Pavlov.

2.2 1958-1965

In 1958, increasing emphasis was placed on the independent development of the country. The program initiated at that time is known as "The Great Leap Forward", and many research programs were established. At the same time, differences with the USSR created problems. Indeed, all Russian support was withdrawn during the years 1959-1960. Nevertheless, a lot of progress was made during this period and a number of basic and applied medical science programs were established in various cities such as Beijing, Shanghai and Canton. With regard to the selection of students, those intellectually most suitable were chosen on the basis of examinations.

2.3 1966-1976

After these few years of rapid progress at all levels, including biomedical sciences, this successful development was suddenly terminated by the decisions taken under the program of the Cultural Revolution. In particular, selection of students was based on new criteria, by the procedure of "promotions" for which the communes were responsible. This promotion system did in general not favour the intelligent and most capable students whose potential was consequently lost to the people. Furthermore, with the reorganization according to the design of the Cultural Revolution, many established institutions were disrupted and their impact on the intellectual development of the country was lost. As a consequence of the Cultural Revolution, a very large gap emerged which will take an estimated 15 to 20 years to be bridged. Indeed, the Chinese pool of scientists and engineers who were able to keep up to date in their respective fields during this period became perilously small.

2.4 1977 to date

After the death of Chairman Mao Tse Tung, the country was threatened by the "Gang of Four". With this danger now eliminated, a new period of modernization emerges under Chairman Hua Kuo Feng and Vice Chairman Teng Shiao Ping.
With regard to the health sciences, an agreement has been signed between the Minister of Public Health, Chiang Yi-Chen, and the Director-general of the World Health Organization, Dr Halfdan Mahler, in which a new program of collaboration is outlined.

The agreement encompasses among other things the establishment of a number of WHO-affiliated research centers in China, the training of Chinese specialists in countries with a high level of biomedical research and the collaboration of established foreign scientists with medical centers in the People's Republic of China as temporary advisors or visiting professors with the function of locally installing biomedical programs of relevance to the country.

This present study has been conducted within the context of the new deal between China and WHO.

3. Present situation regarding biomedical research and health care

This study gives only an incomplete picture of the present situation of biomedical research and health care, since it was not possible, for lack of time, to visit research institutions and hospitals in places other than Beijing.

3.1 Visit to the Institute of Basic Medicine of the Chinese Academy of Medical Sciences, Beijing

This institute comprises three main sections, the first dealing with immunochemistry, the second with immunology and the third with immunopathology. The scientific standard in all three sections appeared to compare well with that of similar institutions in Western countries. The three senior investigators, Prof. S.C. Wang, Prof. A.J. Wu and Prof. G.C. Hou, informed us that there is a lack of younger scientists and students. They also have to work with a limited amount of modern equipment.

3.2 Visits to the Capital Hospital and to the Friendship Hospital, Beijing

In both hospitals, patients were treated with both Western type and traditional medicine. The latter became more sophisticated recently owing to purification of the plant extracts which permits intravenous administration and consequently a more objective assessment of their action.

As in the Institute of Basic Medicine, there was an excellent senior staff of physicians aged mainly between 45 and 70 years,

with an apparent shortage of younger physicians. However, the patient care appeared excellent with regard to diagnosis and treatment of disease. Of particular interest was the good humour of and cooperation with the patients. We were impressed by the very high level of the leukemia program in the Capital Hospital, although there was a space shortage which made it impossible to adequately isolate patients undergoing chemotherapy. The hematology laboratories appeared satisfactory, although lacking modern equipment and some reagents.

4. The needs in the area of biomedical research and health care

Our short visit to two hospitals and one research institute in Beijing obviously do not permit a general assessment of the needs of the whole country in the area of biomedical research and health care. However, the many discussions with competent Chinese scientists and physicians and with members of the Chinese Academy of Medical Sciences were of help in this first approach to the question.

With regard to biomedical research, there appears to be no doubt that the country needs to build up many more research centers in order to guarantee a high standard of tomorrow's health care as well as to have an impact on the medical educational system. The build up of research centers depends less on the present lack of sophisticated equipment than on the lack of recruitment of young scientists. Modern equipment can be purchased but not young scientists.

In as much as health care is concerned, today's general needs appear to be met to quite a large extent with the combined use of traditional and modern medicine. Lack of modern equipment can certainly be remedied without special difficulties. However, the point is to assess in advance the needs which will emerge from tomorrow's general modernization and the shifting socio-economic situation. Vast experience made in industrialized countries has shown that any process which increases the urban population creates a growing need for physicians, generalists as well as specialists. Since the People's Republic of China has formally decided to go ahead with modernization at many levels, there will be, as a consequence, an ever-increasing shift from rural to urban population.

In the assessment of the health care requirements of a modern and more industrialized population, it would seem advisable to study the many causes of the urban threat to health in an industrialized society as we experience it in the West. Furthermore, we see a need for further studies investigating the impact of such an urban environment on human behaviour and on human health and wellbeing. The fruits of such studies by Chinese as well as by foreign scientists (urbanists, sociologists, psychologists, physicians, etc.) should make it possible to avoid many mistakes already made in the urban development in industrialized countries. The health threats, predominantly those endangering mental health of urban populations in the so-called "developed" and industrialized parts of the world, are recognized as due to a great extent to an unsuitable man-created environment. Avoiding such a development in the first place is the big challenge to the health planners of modern China.

5. Recommendations

It is hardly feasible to formulate recommendations based on such a short study tour. The following proposals reflect to a great extent the many discussions we had the chance to have with Chinese experts on the various subjects; to a more modest extent they are based on our own studies and observations in China.

5.1 Medical education

With the present shortage of qualified teachers within the country, it might be desirable to train a certain number of students in excellent medical centers in other countries. If such a program should appear acceptable, the establishment of a list of conditions has to be postulated concerning the recruitment, training abroad, and finally reintegrating students returning from foreign countries. The first and last criteria should, of course, be to create programs according to the country's needs.

With regard to teaching within Chinese medical schools, existing teaching-films (translated into Chinese), as frequently used in Western countries, might be helpful in view of the shortage of teachers.

The WHO Research and Training Center, Geneva, could be of help by preparing concise teaching manuals, one on "comprehensive hematology" and another on "comprehensive immunology". Both manuals would be based on case development with special emphasis on mechanisms of disease, both suitable for independent learning by students during the first years of clinical studies. These short manuals with illustrative sketches and schemas could be prepared in a very near future with the collaboration of the Chinese Academy of Medical Sciences. Additional manuals in other fields of clinical and pre-clinical medicine might also be prepared with the help of WHO.

5.2 Training of young Chinese scientists (post-graduate teaching)

Young scientists in the medical field who have already shown their talents in local research programs could eventually benefit from a stay in a well-established medical center in another country. For this purpose, fellowships could be created for a period of 1 year, extendable to 2, exceptionally 3, years.

5.3 Establishment of new research units and extension of those already existing

For this purpose, exchange of experts between the People's Republic of China and other countries might be useful.

Chinese experts could benefit from a stay of 1-6 months as visiting scientists or visiting professors in qualified foreign medical centers.

Foreign experts could be invited to Chinese medical centers in order to implement programs of relevance.

Such an exchange of scientists would be most profitable if submitted to a national committee responsible for the establishment of priorities concerning health sciences according to the needs of the country's population.

5.4 Science politics in the field of medicine

At a time of rapid expansion of universities in general, and medical schools in particular, it would be of great profit to the country to establish a special Medical Science Council which would have to continuously assess the needs of the people during the process of fast modernization. In addition to suggesting research programs and establishing a priority list for their execution, the Council would also have the responsibility of keeping the government informed about relevant scientific achievements in order to assure their practical implementation without too long a delay, for the benefit of the people.

P.A. Miescher & A. Miescher
26 January 1979

7.3 Second visit to China, November 1979

1979: The second trip to China from 7-26 November 1979 was to provide PAM with an opinion of the health of a huge part of the PRC: Guandong, Guilin, Changsha, Hangchou, Shanghai, Tsinan and finally Beijing again. Our report on the visit is reproduced below:

REPORT ON A MEDICAL STUDY TOUR IN THE PEOPLE'S REPUBLIC OF CHINA 7 - 26 NOVEMBER 1979

1. Introduction

The purpose of this study tour (which is part of a special international programme for developing countries) was to allow the assessment of the health programme of the People's Republic of China (PRC) and to work out ways and means by which the World Health Organization could best collaborate with the country in the development of future health programmes.

The report is based on visits to the following places:

a) provincial hospital of the Guandong province at Guangzhou;
b) commune hospital at Cin Tang, a rural area some 60 km from Guangzhou;
c) dispensary of a production brigade in the same district, with discussion on the health system within production teams;
d) Guilin: discussion on public health problems;
e) Second Teaching Hospital in Changsha and discussion with representatives of this hospital and the medical college of the Hunan University;
f) Shaoshan, with a special visit to President Mao's birthplace (most country houses in this region are still built in the same traditional way with an open fireplace in the kitchen);
g) Hangzhou: visit to the Qiang Yiang sanatorium;
h) Shanghai: discussion with a group of professors;

i) Chao Yang, residential area of Shanghai, with its well-structured health system;
j) provincial hospital in Jinan,
k) Taian, with excursion on Taishan;
l) Capital Hospital, Beijing;
m) Third Teaching Hospital of the Beijing Medical College.

In each city, as well as visiting the various institutions, we discussed health problems with the deputy director of the respective health bureau. Furthermore, conferences given in Guangzhou, Changsha, Jinan and Beijing permitted contact with the leading physicians and scientists of the institutions visited.

2. Health systems in rural areas

We were impressed by the excellent state of health of people of all ages in the countryside during the various encounters we had with inhabitants of rural areas. The system of production teams and brigades has proved to be very successful. The population is organized according to the system of production teams (each team comprising 300-1,000 people), production brigades (each brigade comprising about 10 production teams), and communes (each commune comprising 20 to 30 production brigades). The health care within this basic structure has led to an impressive improvement in the health state of the rural population despite very simple living conditions. Each brigade has a dispensary with one or two "barefoot" doctors and a midwife. The dispensary has special facilities for examination and minor treatments as well as for delivery. The commune hospital (Sun Tong Medical Center) we visited in CinTang takes care of a population of 59,000 people, most of them engaged in agriculture (96%). The commune comprises 193 production teams organized into 24 production brigades. Traditional medicines are prepared in the hospital as well as a number of products such as physiologic saline for perfusions. For the entire commune, there are 25 physicians representing both traditional and Western medicine and 107 medical personnel (nurses, midwives, technicians). Using simple but adequate operation facilities, 400 ambulatory operations and 200 operations on hospitalized patients are performed each year. Besides simple operations, abdominal surgery can be performed at the Commune Hospital (gastrectomy, biliary surgery, hysterectomy, etc.). 1.5% of ambulatory patients are referred to Guangzhou for consultation; 4% of the hospitalized patients are sent to Guangzhou for special diagnostic or therapeutic procedures. There are 90 beds for this commune which has a population of 80,000 (59,000 local population plus 21,000 from neighbouring areas). There are diagnostic laboratories, x-ray and electrophysiologic facilities as well as adequate facilities for physiotherapy.

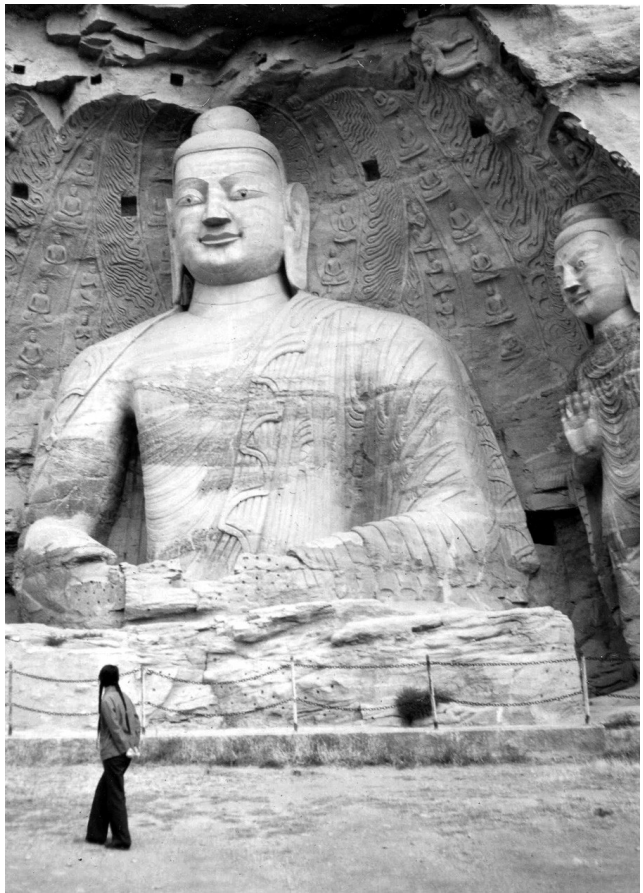
While the present health system gives overall satisfactory results in the province of Guandong, the physicians at the Sun Tong Hospital mentioned the following shortcomings:

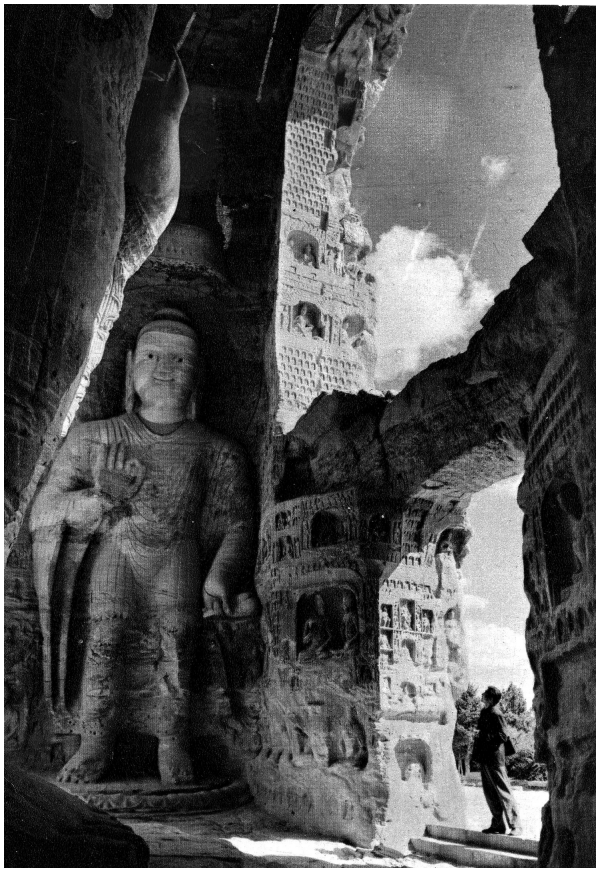
a) there is a need for more qualified personnel, especially physicians:
b) there is a need for better equipment in the laboratories;
c) the Sun Tong hospital is now too small; an extension is presently under construction.

Rural Health 1979

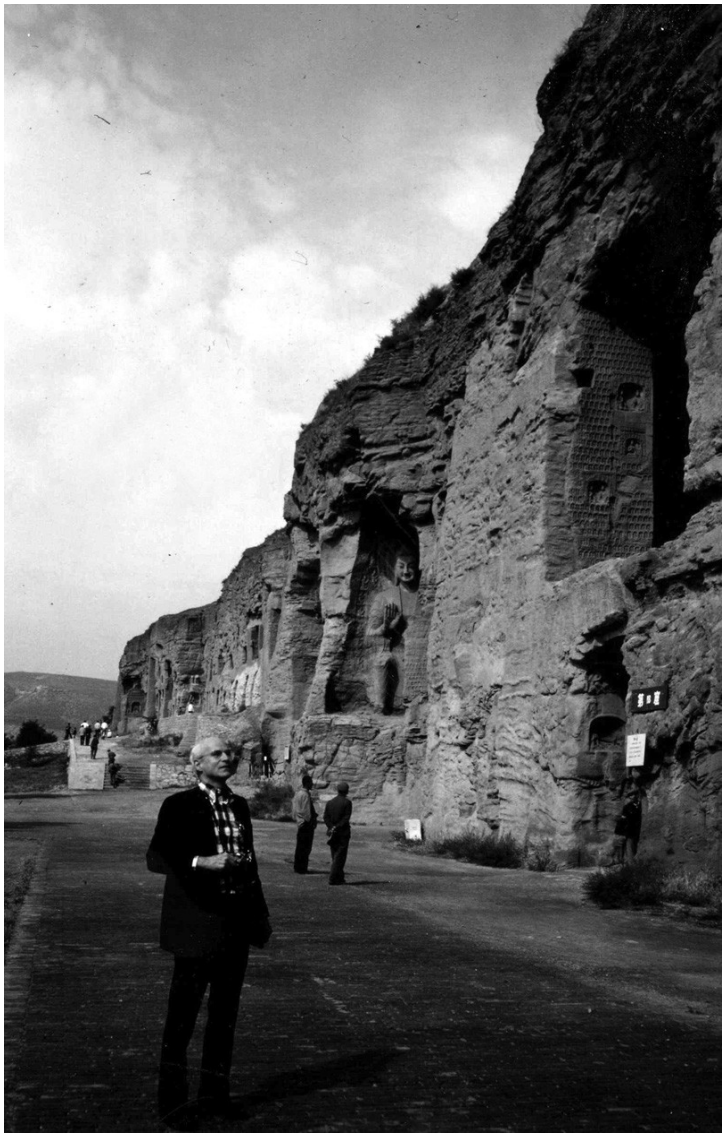
SHAOSHAN MAO' birthplace

Acupuncture





DATUNG, 1979 Yungang-Caves



The prevalence of respiratory diseases among the rural population in the province of Guandong seems to be due partly to smoking and partly to the chimneyless kitchens. Of special concern is a high incidence of nasopharyngeal carcinoma (1,500 cases/year in Guandong province). It is possible that exposure to smoking fires (tar!) in kitchens may contribute to this high incidence of nasopharyngeal carcinoma in certain communes. A possible role of the Epstein-Barr virus is also considered as well as a genetic predisposition. Research on the etiology of this carcinoma is currently underway.

Parasitic infestation of the intestinal tract is also still a problem, although not lifethreatening. Furthermore, drinking water is not yet available in all villages.

Practically all citizens are entered on a health system register.

Each province has its own special problems. In the south, malaria still affects a few million people every year. In some areas, schistosomiasis is still a problem requiring appropriate measures. Furthermore, tuberculosis also represents a health hazard especially amongst the poorer members of the population. In some very poor regions, a major effort is being made to raise both the basic economic condition and the health condition of the population. A special programme has been set up by the Ministry of Health for raising health standards throughout the rural areas, concentrating on the following points:

a) improvement of kitchen facilities, adding chimneys;
b) improvement of sanitation;
c) improvement of sanitation for livestock;
d) environment (diminution and prevention of pollution);
e) drinking water.

Finally, with the improvement of health care in the rural areas, genetic disorders such as thalassemia major remains a problem. In the province of Guandong, the thalassemiabeta gene is quite common. Children with thalassemia major are expected to live longer than three months after birth with improved health care and thus will represent a continuing medical problem. Genetic counseling is necessary to prevent an accumulation of such cases.

3. Health system in urban areas

Health services in cities have been organized in a similar way to that described above for the rural areas. Again, Chinese traditional medicine is used in combination with Western medicine.
A special effort has been made in a number of new residential areas around the nucleus of Shanghai. The Chao Yang residential area has become a model city with a structure designed to give the best living conditions for people in a large city. In this community, different types of activity are well integrated so that the inhabitants can live in a closed society without having to commute to their place of work. The city provides shopping facilities, recreation centres, and schools. There are a number of small factories which permit the people to work within the city limits. One production team we visited was engaged in the manufacture of clothing. Furthermore, the health system is well designed so that the inhabitants have access to dispensaries for preventive health purposes as well as for minor treatment. There is also a hospital in the city. All in all, this city model is a first attempt at forming a closed community at both the social and work levels.
While in this particular "model city" the health system appeared to be entirely satisfactory, we were told that in other urban districts there is a lack of qualified medical personnel and modern equipment. Furthermore, living in large apartment blocks has produced, as in other countries, the problem of alienation because of lack of communication amongst the habitants.
The disease distribution among patients in the Qiang Yiang sanatorium of the Shanghai Railway Association in Hangzhou reflects the rapid appearance of conditions which may be called "disease of modernization". Indeed, the following disorders became increasingly common among urban citizens, especially higher-grade office workers: hypertension, coronary disorders, gastroduodenal ulcers, and neurasthenic states. Smoking appears to be an important contributory factor to respiratory and vascular diseases. Alcoholism, on the other hand, has not become a problem in the PRC, in contrast to other parts of the world. At the Hangzhou sanatorium, in addition to the above-mentioned "stress syndromes", other diseases connected with industrialization were respiratory tract infections, e.g. in the case of locomotive drivers who are exposed to hot and cold temperatures and to draughts. Furthermore, in some industrial areas air pollution also contributes to respiratory ailments.

4. Hospital conditions

All in all, hospitals are clean and patients appear to be content with simple but adequate facilities. Again, qualified medical personnel are lacking. Laboratory equipment varies: some hospitals are rather well equipped, e.g., the provincial hospital in Jinan, others are grossly under-equipped at all levels.

5. Teaching of medicine

Major efforts are presently being undertaken to increase the number of students. The main problem resides in the very big lack of qualified teachers at all levels which is mainly the result of the unfortunate period of the Cultural Revolution. In addition, there is a lack of modern teaching materials. The PRC needs help in the formidable task of quickly training a sufficient number of qualified physicians and teachers.

6. Research

A few nuclei of research are emerging in teaching hospitals and in medical science institutions. In Jinan, we visited a very well equipped research unit studying the ultrastructure of cells with the aid of a Siemens' conventional electron microscope and a Siemens' scanning electron microscope.
In all the medical centers we visited, our scientific colleagues showed a keen interest in immunology. T and B cell analysis, using the sheep cell rosetting technique and the Ig surface technique, was remarkably well done. In Shanghai, studies on the transfer factor proved of little use in the treatment of persistent hepatitis B, a finding which corroborates our own results as well as that of others. There is also a great interest in interferon, which is presently being investigated in various leading medical centres of the world. The fruits of studies of Chinese scientists in Western universities are already apparent. Dr Liu Er Hsian at the Institute of Basic Medical Sciences in Beijing has perfected the culturing of plasmodium falciparum. Furthermore, he uses the hybridization technique for the preparation of monoclonal antibodies to malarial antigens, which he learned in Geneva, more successfully than we do in Geneva. The same encouraging findings were made by Drs Torrigiani, Lambert, Rowe and Rajkovic: Dr Liu Fung Sheng and Dr Chang Chuan-Yi of the Vaccine Institute in Changchun, have reached a level of excellence in the techniques they learned at the WHO Immunopathology Research and Training Centres in Geneva and Lausanne.
Further development of research is made difficult mostly by the lack of young physicians who could qualify as research fellows. We also had the impression that researchers are too remote from patient problems. The subjects under investigation did not always correspond to the need of the patients. In the conferences, we were aware that physicians are often not in touch with their colleagues engaged in clinical investigation. We also found, as in Europe and the USA, a tendency to become engaged in research projects which are of special interest to the investigator without necessarily being a response to a primary patient need.

7. Conclusions and recommendations

Generally, we were impressed by the high standard of the health care in a country which has only been organized since the liberation in 1949. A most complex network of health care has permitted a drastic improvement in the health status of the rural populations. Efforts are presently being made by the Department of Public Health to continue this programme with special emphasis on improving the availability of drinking water, solving of environmental problems, improvement of sanitation, kitchen facilities and livestock amenities.

The health care organization of the urban population has a similar structure to that in the rural areas. While the density of medical personnel is higher in the cities, the needs of the urban population are also far bigger for health care, mostly because of the more stressful way of life within the city.

With the rapid modernization of the country, one sees an increasing number of "side reactions" with regard to the people's health condition. It appears relevant to take into consideration the impact of modernization on the quality of life in order to avoid the disastrous complications which ravage the Western systems.

In view of the increasing need for teachers and physicians, it appears important to reassess the medical educational system and to find the most suitable solution for the PRC. It seems that there is no system in existence in any other country which would be applicable in the PRC.

A number of research units, institutes and centers are emerging where research is conducted at an already quite sophisticated level. The time is right to structure these various research endeavours in an attempt to increase their efficiency. We think that the PRC has reached a level where it is possible to adopt a long-range science policy to meet the expectation that within 10 years major advances will be made. With this outlook, it is very important to undertake every possible effort to coordinate the various research endeavours and thus make them more effective.
Taking the above comments into consideration, we suggest the following recommendations:

7.1 Central Science Policy Committee

Starting at the top level, it would appear to be helpful for the future of medical research to set up a committee responsible for establishing a sound science policy. The function of this committee would be to decide priorities responding to the most urgent needs of the people. Furthermore, this committee would have to ensure that the various research endeavours are conducted in a well-coordinated fashion to guarantee maximum efficiency. One should also emphasize the need for patient-oriented research with investigators constantly keeping in touch with physicians.

7.2 Support of Research Efforts

A few centers of medical research have already demonstrated that Chinese investigators have special skill and endeavour in the performance of their work. For this reason, it appears particularly important to help this medical research where there is a lack of manpower, especially with regard to qualified scientists, and a lack of scientific equipment. It also appears important to develop better research management, particularly concerning coordination among various centers.

7.3 Post-graduate Teaching

For the time being, post-graduate teaching appears to be very incomplete. Young investigators might be trained not only with the objective of becoming established investigators, but also with the aim of gradually building up a post-graduate teaching programme. While graduate teaching is mostly focussed on a sound basic knowledge necessary for the practice of medicine, the post-graduate teaching should deal with the various disciplines in greater depth. In this regard, the existing exchange programme, which is based on the memorandum of 5 October 1978 between WHO and the Ministry of Public Health of the PRC, could be further developed with the following double objective: training of scientists responsible for the post-graduate teaching programme, and preparing the young scientists with regard to their research programme. Experience in other countries has shown that it is advisable to carefully select young scientists for fellowships abroad. Only those Chinese scientists who have already shown their talent in a research endeavour at home, working on a problem of domestic importance, should be selected to join a research center in Europe or USA in order to develop their respective research programme in more depth. Sending inexperienced physicians to foreign research centers is likely to produce more problems rather than to help improve the health status of the Chinese people. Within the scope of this exchange programme, one might also place emphasis on recruiting young foreign scientists for the establishment of new programmes within the various medical centers of China, according to the particular needs of the PRC (the science policy committee could be helpful in defining these needs). A three to six month stay should be sufficient for the foreign experts to implement a new programme.

It might be useful to establish two or three post-graduate teaching centers, with possibly one in Guangzhou, one in Shanghai and one in Beijing. These teaching centers might then be used for further training, with special courses, of young physicians from other medical centers. The science policy committee mentioned in 7.1 could be helpful in formulating the priorities of the various post-graduate teaching programmes.

7.4 Graduate Teaching

With regard to the training of students as future physicians and teachers, we think that WHO might be of help in arranging for the preparation of manuals, according to a uniform structure, by experts. In particular, the text should be prepared in such a way as to develop diagnosis, clinical picture, and treatment of disease in function of the underlying pathogenic mechanisms. Furthermore, the various authors would be instructed to emphasize problems of practical interest and to avoid dwelling on extremely rare though interesting conditions. With the diffusion of such manuals, the training of students would probably become more efficient that by sending selected students to foreign countries. In addition to these manuals, the use of films has proved to be an efficient tool if properly introduced and commentated. The PRC has already prepared seven teaching films of very high quality. WHO might also collaborate in the preparation of new films. With regard to the curriculum for Chinese students, this again must be tailored to suit the particular needs of the PRC.

WHO might be of help in supplying audio-visual teaching material for Chinese medical students. This type of teaching has proved particularly effective in anatomy, pathology, hematology and dermatology.

7.5 Literature Service

WHO could also be of help in the establishment of a literature service by diffusing special publications. Existing journals which summarize recent developments, such as the various Seminars series, could be translated into Chinese with the help of WHO (special arrangement with publishers). Existing WHO booklets could be adjusted to the needs of the PRC. Furthermore, WHO could be of help in the establishment of reference libraries in two or three medical centers.

7.6 Research Centers on Human Behaviour

Past modernization programmes in other countries have led to the appearance of side reactions concerning mental health. In future programmes, especially concerning urban development, it should be possible to reduce these reactions and in particular it should be possible to avoid the unfortunate developments seen in Western countries by a planning which takes into consideration basic human behavioural patterns. In order to guarantee sufficient experts in this field, it might be desirable to set up one or two research centers to study human behaviour with particular emphasis on living conditions in urban areas. The aim of such research centers would be to learn to design urban developments which maintain or increase the quality of life of the inhabitants. The experts trained in such centers would also need to collaborate with architects and ecologist within the overall modernization programme in an attempt to best serve the people.

7.7 WHO Liaison Committee

In order for WHO to be able to respond quickly to the needs of the PRC, it would appear desirable to set up a special committee composed o 3-5 experts from an area around Geneva, plus one expert from each of the following countries: Australia, Canada, United Kingdom and the USA. This committee would communicate directly with the Chinese committee on science policy. It would be the WHO liaison committee's responsibility to quickly respond to the needs formulated by the Chinese science policy committee. This committee would also ensure the coordination of the various efforts presently being undertaken within WHO. The following divisions of WHO are currently engaged in special programmes for China: (1) the Immunology Unit under whose guidance a special technical visit to China has just been made from 13 to 23 November 1979; (2) the division of Parasitic Diseases (malaria, schistosomiasis); (3) Special Programme for Research and Training in Tropical Diseases; (4) Special Programme for Research and Training in Human Reproduction.

7.8 Memorandum of Understanding

The recommendations expressed in this report are in line with the "Memorandum between the World Health Organization and the Ministry of Public Health of the People's Republic of China Governing Technical Cooperation in Health Activities" (5 October 1978).
Professor P. A. Miescher & Dr A. Miescher 15 January 1980

7.4 Third visit (meeting with Minister Quian-Xinzhong) : Recommendations 1981.

1981: Just 24 hours in China with Dr Thomas Lambo, assistant director-general of WHO, Geneva on 6 June, to establish a special WHO program for the PRC. This program is reproduced below:

1981
PEeter A.Miescher
Minister of Health
Dr.Th.Lambo,WHO

THAI plane in Typhoon

Pakistani air-hotess

With the Minister of Health of PRC
XIAN "BUDDHA" 1981

SPECIAL WHO PROGRAMME FOR THE PRC (6 JUNE 1981)

The Ministry of Health of the PRC is presently engaged in a tremendous effort to modernize the existing health programme at all levels, from the training of physicians up to research and development. The dimension of the programme is such that the Ministry of Health needs, in addition to the help from the Western Pacific Regional Office of WHO, support to efficiently go ahead with the modernization of the existing health programme. Thus, the purpose of this special WHO programme is to efficiently assist the Ministry of Health of the PRC in the development of the public health programme in a period of rapid changes, both current and prospective.

Objectives:

The main objective of this programme is to increase or maintain the physical, mental and social wellbeing of the people in a country undergoing rapid industrialization.

Ways and means of reaching objectives:

At the present time, the Ministry of Health disposes of a large advisory panel comprising some 300 scientists. In the discussion with the Ministry of Health on 6 June, it was thought it would be advisable to set up a special committee which was small enough to be effective in fulfilling the following functions:
a) To continuously define the changing needs of the people in various parts of the country with regard to preventive and curative medicine. Teaching, biomedical research and research in the field of mental and social health should be adjusted to these changing needs.
b) To establish priorities concerning graduate and post-graduate teaching as well as research and development.
c) To ensure that the increasing number of projects are well coordinated.

It was thought that the committee should have less than 20 members in order to be able to reach decisions efficiently and effectively.

At the meeting on 6 June, it was suggested that it would be useful to set up a special Geneva-based committee for this programme with corresponding members in Europe, USA, Canada and Australia. The function of the committee would be to quickly respond to the requests from the Ministry of Health in arranging an exchange of scientists as well as in quickly giving expert advice whenever needed.

Special orientations:

In the planning of the modernization of the health system in the PRC, it was considered that as much could be learnt from positive accomplishments as could be learnt from mistakes. With the period of under-achievement during the Cultural Revolution, the PRC has the possibility of avoiding the enormous mistakes made by the industrialized countries and which will take decades to remedy.
One of the major negative developments in industrialized countries has been the deterioration of mental health and social wellbeing. With rapid industrialization, experience in Western countries has clearly shown the difficulty in distinguishing between "real" human needs and "desires" created by consumer products. In advanced industrialized countries, it has become evident that companies create new markets but not necessarily to the benefit of the people. An old Chinese proverb says: "Beware of what you desire; you may obtain what you want and then have to live with it."
Conditions for physical, mental and social well-being rapidly change with any modernization programme. While the industrialized Western countries directed all their efforts to the physical well-being, the neglect of mental and social aspects of health has resulted in a very inefficient overall health system, as measured by the final goal, which would be a good degree of health in the global sense.

Institutes of mental and social health

In order to avoid a similar development within the PRC, it was considered advisable to set up institutes of mental and social health. Such institutes may also be concerned with the problem of human reproduction. Dr Qian-Xin Zhung actually had an excellent idea in suggesting that funds allocated for the creation of two institutes of human reproduction be used for this purpose.
At the discussion in Beijing, it was clearly acknowledged that such institutes would represent a total innovation in terms of public health policy. In order to ensure that the benefits of the work carried out in such institutes is rapidly made available to the people, it is important to establish, from the beginning, connections with other governmental organizations.
To reach one of the main goals of education in terms of helping the child to become well integrated in his society (social wellbeing), studies on human behaviour in an industrialized society appear of great importance. For this reason, connections are necessary between these institutes of mental and social health and the department of

education. In Western countries, moral issues are being increasingly neglected in schools and institutes of further education. It now appears that moral structures are essential for mental and social wellbeing. This conclusion is not new since Confucius already emphasized the need for setting up side-by-side a legal and moral structure for the wellbeing of the population. In Western countries especially, ethical structures based on human obligations are being increasingly replaced by antithetical structures based on human rights. This development appears to be very dangerous for the mental and social wellbeing in favouring isolation and alienation of individuals. It would be the function of the institute of mental and social health to set up, together with the education department, baselines for the education of children, helping them to integrate themselves into the modern society.
The institute would also need intimate communication with the department of agriculture. Equilibrium between the rural and urban population has always been important for the wellbeing of a population. Uncontrolled "industrialization" of agriculture may have disastrous consequences in terms of mental and social health.

Department for urban development:

Urban development which does not take into account human needs in behavioural terms, has already proven to be detrimental to the quality of life in most modern cities. A few pilot studies already exist to show the way t avoid mistakes in this domain.

Timing
In the discussion in Beijing, it was considered advisable to go ahead without delay with this programme and a first meeting for the selection of the Geneva-based panel has been suggested.

P.A. Miescher

7.5 Fourth visit to China (1982)

1982: In early September, 1982, first of all a series of conferences in the USA: New York, Houston (Blaffer visiting professor at the MD Anderson Tumor Clinic), Seattle (Immunology Congress), flying in horrible typhoon weather with the marvellous Thai airline to Tokyo-Narita airport, where all flights were grounded, but luck was with us and we were able to jump into what must have been the oldest Pakistani aircraft in existence which carried us safely to Beijing, arriving on 13 September.

Near to our hotel was the "tavern" for high-ranking politicians and their guests, on one of the upper floors at a discreet distance from the loud crowds below. Here, a most elaborate table had been set for 12-14 people. We were rapidly introduced to all those present since the cooks seemed to have timed to the minute a sumptuous dinner which was served at incredible speed. Everyone was apparently ravenous and the marvels of Chinese traditional cooking were devoured as soon as they touched the plates! The movement of the chopsticks was interrupted only by the exclamations of "Kampè" as the highest-ranking official raised his little glass of rice-wine. At 8 o'clock, everyone stood up, and with a brief nod of the head and "she-she", the ceremony was over.

We must name our famous hosts, whom we will remember for ever: the Minister of Health, Qian Xinzhong, his wife and professor of psychiatry, Shen Yu-tsen, Professor Ch'En Wenchieh (hematologist), his wife, Dr Liu Juan, both from the Beijing Academy of Medical Sciences, Professor Teng Chia-tung, nearly 90 years old and teacher of Ch'En and also from the Academy of Medical Sciences, Professor Lu Dao-Pei from the Institute of Hematology and People's Hospital of Being Medical College, Mr Ang Jun-feng of the Foreign Affairs Office, Ministry of Health (and later our wonderful guide to many, many places), as well as Dr Fang-chi (cardiologist), Professor Chang An (hematologist), and Professor Hou Yu-hua, hematologist, all from the Capital Hospital.

We returned to the hotel accompanied by Mr Wang. It was 9 o'clock and already dark. Nobody locked their hotel room door as in those days Beijing enjoyed total security. The next morning, at about 4 o'clock, we were woken by the discreet noises of horse-drawn vehicles in the street below. It was the "night soil" being carefully collected and then taken out of town to the agricultural zones where this fertilizer was highly appreciated. At this early hour, it was still quite dark, and we soon started to see hundreds of cyclists in their blue uniforms heading in all directions to their places of work. The temperature was about 10°C, but many cyclists covered their mouths and noses with a sort of white filter.

The next day, we visited the Tong-ren Hospital and met Professor Zhao Xia-yin (the boss of You-peng Huang who was at that time working in the Hematology Division at Geneva University Hospital), and with the president, Professor Dia. At dinner, we were the guests of the Ministry of Foreign Affairs, Ambassador Yu Pei-Wen, his wife Ghu Zhong and Minister Qian Xinzhong.

A huge programme was planned for Peter and gives an idea of the confidence that the Chinese authorities had in him, and also how eager they were to have our further opinion and advice with regard to the health situation in their country.

Travelling by train all through the night, we arrived in Datung (Shanxi) at dawn. It is one of the main coal mining areas and the whole city was covered with a black-blue film of coaldust. After a breakfast of the best raviolis and tea, with Mr Wang we visited the Yunkang caves (more than 50 of them), some 5 miles distant from Datung, cut into a stone slope extending horizontally over about 300 metres. This "wonder of the world" of Buddhist religious art, dating from the Wei dynasty (5th and 6th centuries) shows thousands of statues of Buddhas, musicians and angels.
Continuing with the railroad to the industrial city of Taiyuan and admiring the unforgettable landscape of the driest places possible for farming which suddenly become green and flat.
Here PAM gave lectures at the 2nd affiliated hospital of the Shanxi medical college. Professor Jan Chia-yen, the mother of Zhan Ziahong, who later trained in the WHO unit at Geneva University Hospital, was the leading clinician in charge of our visit to Taiyuan.
To compensate our professional efforts, we were driven by car over mountain roads to the Wutaishan mountains in the north-east, about 130 km away, where we visited some wonderful Buddhist monasteries hidden throughout a narrow valley, dating from the late Tang and Sung dynasties. (These mountains, which reach nearly 3000 m, are sacred to the Mongols. Of the many hundreds of original monasteries, only about a dozen remain!). We spent one night in a lodge and we awoke to find that snow had covered the landscape. Our trip continued to Dian, first many hours by train down the Fen river valley to the confluence with the Huan He (Yellow) river, then the train turned West along the Wei river and we were in the old Changan (Xian - in earlier times called Great Peace), one of the oldest and most interesting towns in China, on the old Silk Route. Here, Peter again gave conferences on autoimmune diseases, particularly rheumatoid arthritis and lupus. On a nearby hillside is the as yet unearthed tomb of the unifier-emperor of China, Shi Huang-di. However, already unearthed are the 6,000 terracotta warriors, some on horses, all dating back to the years 221-209 B.C. The Tang and the Ming dynasties also left their imprints here. In a nearby monastery are the oldest Buddhist sutras brought by the monk on his back to China, about 100 years after Christ we were told.
After 3 days, we continued by train to Sechuan Province, 24 hours all the way. In Chengdu, we met Deng Chang-an, the famous internist and boss of our future pupil, Tang Hua-yang (now an oncologist at New York

University). Chengdu is on the Min river, has an irrigation system more than 2,000 years old and, like Xian, has a population of 2 million. It lies in a zone where harvesting is possible 3 times per year. Peter gave speeches on blood dyscrasias and Sjogren's disease, a frequent autoimmune disorder in Sechuan. Again, with a 26-hour train-ride, we went to Yunan Province. Travelling through the lower Himalayas with their colourful minorities (seen from the train which often traveled at 30 km per hour). We had the same sobas (noodles) three times during the journey and, every time they were reheated, they became several shades darker. Nevertheless, we arrived happy and well on 28 September in Kun ming, the provincial capital in south-west China, with a medical college and about 1.2 million people. Its affluence dates from 1910, when the railroad to Hanoi was built. The town has a mild climate and is situated on a beautiful lakeside, but the rich mineral soil has led to some ugly industrial development.

We flew home via Guangzhou and Hong-Kong to Geneva. Less than 4 weeks had gone by!

Report on a medical study tour in the People's Republic of China, 13 September-4 October 1982

1. Introduction

The purpose of this trip was to assess the progress achieved in the health system of the PRC since 1978 and to analyse the impact of the modernization programme on the overall health of the population. Our trip covered a large sector of the country and included Beijing, Datung, Taiyan, Xian, Cheng-Du, Kunming and Guangzhou.

2. Overall impressions

In comparison with 1978, we noticed that the vast majority of people appear more content and confident for the future. In general, they look healthy, well fed and in good physical condition. Clothing has become more individual yet with a very decent appearance, reflecting the good taste of the people and the will to conform. The shops provide a larger variety of goods and the people can obtain, in general, what they want to buy. There are no vital supply shortages. Those people to whom we spoke showed a very mature socioeconomic attitude towards public affairs. They have realized the importance of accepting that personal wellbeing must be matched by the wellbeing of the general population.

As an expression of the good quality of present-day life in the PRC, we saw a very large number of Chinese people, from the city as well as from the countryside, visiting historical monuments and places of interest, the overall atmosphere being very relaxed and enjoyable. The children were never aggressively exuberant or violent, but cheerful and well controlled.

2.1 Cities

The development of new housing areas is very impressive everywhere. When questioned, people are very proud of this development and hope for an improved standard of living in the new apartment buildings. Not yet apparent are the side reactions seen in certain western cities where the urban dwellers obviously suffer from overcrowded living conditions in a dehumanized environment, though some Chinese cities are starting to look here and there like modern western towns.

One of the first consequences of dense urban living conditions within small, isolated apartments appears to be the acceptance of strict family planning with, ideally, one child per family. In this respect, it is interesting that most couples prefer boys to girls as only children. It is too early to assess problems which may emerge from the "one-child family".

2.2 Countryside

Since we travelled nearly 2,000 miles by rail and car, we came into good contact with the countryside. There is a visible change concerning the way peasants work the land. We saw less group work and more individual effort. Watching the peasants at work, we were struck by their contentedness, the increased hours in the fields and the care with which they perform their tasks. This new pattern is a consequence of the distribution of land to the peasants which has been carried out in many provinces. We were told that this new system has led to a considerable increase in productivity and consequently also to an increase in prosperity. This increase in the standard of living is seen not only in the contentedness of their children, but also in the peasants of the free markets everywhere, who seem very satisfied. Most young people are cheerful, well-fed and visibly enjoy their life.

For obvious reasons, family planning is less well accepted in the countryside where children (mainly boys) have always been essential to participate in family work and to continue on the family land once the parents are too old to work.

On the way to Kunming, we had the opportunity to observe various minorities who appear to enjoy their special status, wearing their traditional costumes with pride, though their living standards seemed somewhat below the average.

3. Impact of the modernization programme on human behaviour

3.1 In the city

For the time being, people appear very content. In Guandong Province, we were impressed by the peaceful enjoyment of large numbers of people when the 15' October celebration coincided with the moon festival. There was a happy gathering together of people with cheerful communication amongst the various groups. There were no signs of people suffering from isolation or exclusion.

People have become eager to have a modern home. This desire facilitates the urban planning centred on the need to provide maximum housing surface to a minimum of ground space. The severe side reactions to such a development which have been observed in Western Europe, Japan and the Americas are not yet apparent. However, the first symptoms are emerging as illustrated by a comment made by Mr Zhao Xijie from Cheng-du. Mr Zhao told us how much he enjoyed his youth in a rather simple and old complex which housed 10-12 families around a common courtyard. All the social life from childhood to adulthood happened in this meeting place which gave Mr Zhao a feeling of social well-being and belonging. It was within this framework that he made many friends in this small community he could identify with. He also had the opportunity as a child to encounter the older generation who had a big influence on the children. In addition to being useful in supervising the children, the old people usually reflected a wisdom about life which Mr Zhao found important for his growing up. It is interesting that Mr Zhao recognizes the fact that the present construction of large modern apartment blocks does not provide the structure necessary for a feeling of togetherness. He realizes what is plainly being felt in the more "developed" countries, that the small apartments will probably remove the older people from the younger generation. Furthermore, he already assesses
the danger of alienation arising from the anonymous atmosphere of large apartment buildings. This development is especially serious at a time when the number of children has to be drastically reduced in order to control the size of the population and where insufficient space is planned for the purpose of "human communication" within the closer as well as the larger circle of family (grandparents - parents - children, etc.), the closer community of friends and the larger community of people living together. However, Mr Zhao and other officials concerned with urban planning stated that, for economic reasons, it seems difficult for urban planners to take into consideration psychosocial needs other than the bare essential ones for a family of three.

3.2 Impact of modernization on the rural population

The situation in the country has also greatly benefited from the modernization programme as reflected in an increased feeling of wellbeing among the people we saw along the way. Modern apartment buildings are the exception. The traditional way of living in small villages with a group of 400 to 600 people provides an ideal framework of social life. Villages are well delineated providing a feeling of security to the inhabitants, all of whom know each other. We were told that the distribution of land has been very much appreciated and consequently has been successful in most parts of China, with the exception of special parts where the peasants' work continues along the lines of the previous structure with the organization into production brigades and production teams. The latter organization has proved successful in parts of the country with very poor quality soil where the peasants prefer to share the inherent risks. Also, a more organized work force has been found to be beneficial where the mechanization of agriculture has become necessary in order to increase the productivity of the land, for instance around Beijing.

We had no opportunity to assess the impact of heavy industrialization of agriculture on the quality of life of the peasants. In highly developed western countries, the impact of agricultural industrialization has been double-sided: while the overall prosperity of peasants has increased, the work has become dehumanized. Modern "mechanized" peasants today do more and more work with less and less human help. Even the family work approach is no longer possible with the introduction of heavy machines.

4. Development of the health system in urban areas

The relationship between physicians and patients appears to be very well balanced whenever we have investigated this question. Physicians are aware that their function is to serve the patients. With regard to the patient, this situation is underlined by the fact that the patient has to pay the physician. He may subsequently request reimbursement of his medical care expenses. The patient becomes aware of his responsible relationship with the physician which helps him to play an active role in the cure of his ailment. This sense of responsibility also reminds him of his obligation to preserve his health which helps the overall approach of the country towards programmes of preventive medicine.

4.1 Hospitals in the urban areas

There appears to be progress with regard to the hospital conditions. There is continuous renovation of wards and laboratory sectors in many hospitals. The example of the Capital Hospital shows a fruitful development of certain divisions, e.g. the Division of Clinical Immunology which is likely to become a WHO reference centre for immunological methods.

It is our impression that the main difficulty is still the shortage of qualified leaders, the lack of supplies and the lack of adequate modern equipment. The academic recruitment is rendered difficult by the fact that in some provinces medicine does not seem to attract the brightest students, who prefer to become engaged in the technical sciences in order to contribute to the modernization of the country. Modern laboratory medicine still has a long way to go to reach a good standard with appropriate quality control.

The establishment of priorities within hospitals is very difficult under these conditions. Bright physicians are eager to develop interesting areas without always considering the overall needs of the population. As an example, too many hospitals are eager to set up bone marrow transplantation units. In the interest of the people, one well-organized unit in Beijing would be sufficient in the beginning to develop a bone marrow transplantation programme for a population of 6 to 7 millions. Setting up more than one unit would mean dispersing the efforts. It is far better to have one good unit than two or three inferior ones. Similar mistakes have been made in many parts of Europe where, sometimes at tremendous cost, little has been achieved due to lack of concentration of effort in particular ventures.

4.2 Teaching of medicine

The number of medical students has very much increased over the past few years. Many senior staff members are now teaching medicine according to the modern concept of explaining mechanisms of disease. However, the main problem is the insufficient number of teachers.

4.3 Research

Our colleagues in Beijing are very keen to introduce modern methods for clinical research. Two main difficulties have been mentioned to us. The first is the lack of modern equipment and supplies; the second is the lack of coordination between the various research centres in China where work is being done on related subjects resulting in duplication of effort and waste of money and energy.

5. Rural medicine

The Chinese organization of rural medicine has been highly successful with each production brigade having a dispensary with one or two barefoot doctors and a midwife, and with commune hospitals for about 24 productions brigades. With the distribution of land to peasants, a number of organizational difficulties arose. One of the major problems is the fact that a barefoot doctor now makes a financial sacrifice in not being a peasant. In a few provinces, many barefoot doctors have actually preferred in more recent months to work as a peasant rather than as a "doctor". As a consequence, there is a shortage of barefoot doctors in different parts of the country, mainly in the province of Yunnan.

6. Discussion

All in all, we were impressed by the progress made by the Chinese people over the past four years, resulting in a high standard of mental and physical wellbeing.

With regard to "physical health", China has become a model of an excellent organization of primary health care. In particular, the role of traditional medicine has proved most useful and efficient in maintaining the overall standard of physical health. The present shortage of barefoot doctors underlines the importance of the system, and we have been told that the necessary steps have already been taken to remedy the situation.

The implementation of western-style medicine poses three main problems: the first concerns the modern hospital infrastructure which requires the establishment of clinical sub-specialty units and the setting up of general and specialized laboratories; the second concerns the training of students, and the third postgraduate teaching.

Modern medicine has developed in such a way that it has become necessary to set up clinical sub-specialty units with appropriate laboratory facilities. This is made difficult by the lack of qualified physicians and the high cost of setting up new laboratory facilities. Results of successful attempts could be seen at the Capital and Tung Jen Hospitals.

With regard to the training of students, their number has increased as has the quality of teaching, but the lack of qualified teachers still poses serious problems. The study of foreign literature, especially in English, has been introduced with considerable success to help remedy the shortage of teachers.

Postgraduate academic training is one of the most acute problems. For successful postgraduate training, one would need well functioning sub-specialty units with appropriate research facilities. Since this structure is only in its initial stage, it is difficult to recruit students for postgraduate academic careers. The situation is made worse by lack of financial resources for supplies and equipment without which it is impossible to set up modern research units.

Major efforts are necessary to remedy this situation. Primarily, it is essential to establish priorities in order to concentrate efforts according to the specific needs of a given area (selection of specialized laboratories, selection of research projects, etc.). Once these have been established, efforts should be coordinated at all levels, i.e. between universities, between hospitals within a city (not every hospital needs all possible laboratory facilities) and coordination of research activities within a university hospital. With the ever-increasing cost of modern medicine, it is important to set up new developments, whether diagnostic and therapeutic units or research projects, to suit the needs of the population rather than the interest of the investigators (focusing on the practical aspects).

In order to remedy the lack of appropriate postgraduate training opportunities, an increasing number of young Chinese scientists have been given the possibility to study abroad or to become engaged in research programmes in USA or Europe. However, if they do not have a specific programme upon their return to China, they will have to face the same problems as young European scientists in the post-war period who were given the opportunity to work in American universities. These young scientists were frequently sent abroad without selecting their research activities according to the needs of their home country. Many of them never returned home, thus causing a great loss of scientific potential to their respective country. The lesson to be learned from this lack of sciencepolitics "at home" is obvious: before sending a research fellow abroad, he must first work on a research programme at home, tailored to local needs. The training abroad would then be focused on these very needs giving the candidate the right motivation to return home once his stage abroad has been completed.

Regarding mental health, the PRC may have a unique chance to avoid the mistakes made by the western industrialized countries. For the time being, the Chinese people appear to have an amazingly high standard of mental well-being, compared to the rather low level prevailing in western industrialized countries, where mental health is compromised by the side effects of industrialization and modernization. However, the first side reactions to urban planning carried out by focusing mainly on technical questions without taking into consideration basic human behavioural attitudes and needs are just starting to emerge in China. Local authorities claim that, for budgetary reasons, it is not possible to orient urban development to standards of human behaviour. However, if one assesses the price western countries are paying and will continue to pay in order to remedy negative psycho-social side effects of modern cities, it would appear more logical and economical to immediately investigate the criteria which should be applied in a modern housing development to prevent the phenomena of psycho-social alienation found in the so-called developed nations. If one considers the importance of mental wellbeing for the overall health of a population, it would appear logical to give priority to research programmes concerned with this aspect of health, especially at a time of rapid expansion of cities.

As mentioned in our 1979 report, it seems desirable to set up research centres on human behaviour in order to help architects to plan housing facilities which take basic human needs into consideration. The aim of such research centres would be to learn to design urban developments which can offer an equitable quality of life to the new inhabitants. A close collaboration between architects, social workers, ecologists and physicians will be necessary to develop urban programmes in the real interest of the people. In such a context, family planning would become an integral part of a project centred on the overall aspects of human behaviour, and in particular on the need for an integrated social life with the participation of all generations and also of the invalid.

In this context, we would like to quote a statement made in a recent WHO report of the Scientific Working Group on Stress, Lifestyle and the Prevention of Disease: "Urban expansion is often either unplanned or planned only for economic interests, with little concern for human factors and quality of life. High-rise apartment buildings, because of their economies of scale, are often preferred by public housing authorities over smaller or more traditional housing units although they are know to provide a poor psychosocial environment for child development. They isolate family groups from one another and are particularly stressful to the elderly and the handicapped, who suffer from acute isolation and even abandonment".

CONCLUSIONS

While primary physical health care in China is a model of an efficient system which has tremendously increased the overall level of physical health, the development of westernstyle medicine for specific physical health problems still has a long way to go. In this latter development it is essential to carefully set up priorities and to well coordinate the efforts necessary for the modernization programme without wasting time and energy.

With regard to mental health, the first signs of alienation within the urban population could be detected in some cities, but the overall mental wellbeing still appears to be undisturbed. The traditional Chinese culture has been preserved until the present day, but it should be further preserved in order to avoid the disastrous effects on mental health which have been caused by industrialization and modernization in western countries (Lu Rushan). It is to be expected that mental health will become an increasing problem if the modernization of the country proceeds uncontrolled. For this reason, among the various developments in the health sciences, the one oriented towards the mental well-being gains in importance, especially with regard to the urban population. The example of western industrialized countries has shown that the enormous expenditure on physical health aspects did not prevent the degradation of the mental health.. The PRC is now in a position to learn from the mistakes made in other industrialized countries where urban developments were carried out without taking basic human behavioural needs into consideration. It would appear essential to set up research centres on human behaviour oriented towards urban living conditions. One of the principal aims would be to study the conditions necessary to provide an enjoyable psychosocial climate for optimal human communication (physical facilities for recreation and for joint activities of a society of different age groups and composed of small families).

Peter A. Miescher, MD
Annatina Miescher, MD

7.6 Fifth visit to China (1986)

On 1 March 1986, Peter was made Honorary Professor of Beijing Medical University on the recommendation of Drs Shen Yu Tien and Lu Dao-pei, professor of hematology at the People's Hospital. On 10 March he was honored by the Beijing Academy of Medical Sciences. Following these award ceremonies, Peter gave lectures on various immunological and hematological topics and was asked to comment on selected patient cases. We remember, for instance, a beautiful girl of 16 with questionable cerebral lupus, as she was completely unresponsive but in perfect physical health, dressed as a ballerina!

We then went by train to Tianjin, a town southeast of Beijing with a population of 5 million, three universities and one medical college. It is an industrial town, renowned for its carpet industry but which also has food-processing plants, iron works, car factories, etc. However, our reason for being there was a conference to be given by Peter in the largest hematology and transfusion center in China, where our old friend from the Geneva Mission, Professor Ch'En Wen-chieh, was the "imperial" director, since his huge frame and quick eye could not be missed. He was surrounded by an adoring "harem" of female scientists and his quiet and cerebral wife, Dr Liu Tuan. When we left the third largest town in China we took with us a nice carpet we had bought.

7.7 Sixth visit to China (1988)

In 1988, Minister Ch'En Min Zhang invited the Mieschers to make another Far-East conference tour, and on 11 April we left Geneva to travel via Frankfurt to Hongkong. We arrived in Chengdu in the late evening of 12 April. The delay was due to the fact that the airport of Guangzhou was completely clogged with people, all flights being over-booked, giving us a feeling for what lay ahead for this rapidly developing country. It was already dark, we had been travelling in all for 24 hours - from one morning to the evening of the next day, jet-lag unknown, since were driven quickly to the Mei-Shan Hotel (named after the holy mountain of Sechuan). During this 3-day stay in Chengdu, Peter gave 4 long lectures followed by discussion. Students participated far more freely than during our earlier visits; there was great interest in being able to visit the Western world. The conference topics were SLE, Sjogren's disease, RA, blood dyscrasias such as myelo-monocytic leukemia as well as hemoglobinopathies. The audiences' knowledge of most of these subjects was rather limited, which made the confusion in the discussions quite difficult to dispel. The main problem was one of communication due to the poor English of most of the audience plus the lack of English-language scientific publications, even though the library had Seminars in Hematology (founded by PAM) and other scientific periodicals and books (Sechuan is one of the more affluent provinces, with rich agriculture and sufficient water thanks to the Himalayas to the west). We of course saw the zoo with the pandas eating fresh bamboo sprouts. We were shown collections of the raw materials used in Chinese traditional medicine: for example, deer horn, several kinds of mushrooms, herbs, turtle shells, etc. that were to be found on open market stalls, near monuments and old temple sites where incense burned all day when it was not raining. The president of the West China University, Ze Yi Cao (obstetrician), the vice-president (a professor of pathology) and our old friend Deng Changan (professor of medicine), and four other members of staff, were always at our side, not forgetting young Tang Huayang, who spoke the best English of them all and was indispensable for our discussions as an unobtrusive, quick translator.

On 16 April, we rose at 5 o'clock in the morning to be ready for Chinese Airways flight 4331 but had to wait 2-3 hours as delays had become normal in those early days of the tourist boom. At noon we landed in Changsha, capital of Hunan Province, which we first visited in 1979 and where, apart from being there officially to give a conference on immunopathology, we would visit our pupil, Professor Shi-shi Guo, who had worked in our Geneva group for about two years, and were even invited to his home where we also met his wife and young daughter. In the same historical neighbourhood was the house of Professor Huang, a famous surgeon from the time of Sun Yatsen, now nearly 90 years old, a tall man with an impressive head (Huang = yellow, the emperor's colour; he was indeed related to the imperial family). His son, from a second marriage, is our pupil Huang Yu-peng, and his mother, a youngish little lady,

served us tea. It was very pleasant to meet up with friends from Geneva.A quick look at the more than 2,000 years-old mummy of the Han princess, wearing a silk dress and with pitch black hair framing her fat white face, reminded us that this city of 2 million people has an important history: not only Mao but also many other illustrious people were educated there.

Rice is the main crop and the spices served with it are so strong that you immediately weep, unless you are PAM who must have Hunan origins... At 08h20 on 20 April we were ready to start our train trip to Beijing, but could only get our tickets validated after secretly pushing a bunch of paper yuan into the ticket inspector's pocket. PAM was soon asleep in the upper level of our compartment; I was sharing the downstairs with an old farmer who throughout the long trip, insisted on giving me some of the cooked eggs his wife had carefully provided for his "survival", eggs not only from hens but also from geese, ducks, snipes, pigeons. It was only when I stopped saying "she-she" and invented the sound "glug-glug" that he realized that I had transformed into some sort of Papagena!

During the more than 24-hour journey (about 1,000 km), from the train we saw rivers and pagodas, charming villages, smoking chimneys, oxen pulling ploughs in rice paddies, very few signs of industry but some construction sites of huge buildings all using bamboo scaffolding. Our best views of Chinese life came from stops at railroad stations. In the past, few private citizens traveled by rail; soldiers or other uniformed men, all smoking throughout the journey, filled the trains. Now, in 1988, many compartments were jammed full, with many people, including women, having to stand. They traveled with lots of bundles and pieces of luggage, even on their heads, some had a goose with them or a cage containing guinea pigs or rabbits. As most of the people traveling were of the Han ethnic group, they were all clad in blue or khaki, the women all wearing trousers, but in contrast to 1978/79, their hair was now cut short (the beautiful long tresses probably sold), only the children could wear colourful clothes and fancy hairdos. By this time, the "one child only" policy had led to these only children being called little tyrants, eating too many sweets, their milk-teeth black with caries and their smiles sad to see. This phenomenon was unknown in 1978/79 as people, particularly in the north, never touched sugar apart from the sweet dumplings at New Year or on 1 October. People were now growing fatter, adults and children, whereas before we had seen only elegant silhouettes. Peter woke up hungry but, not tolerating eggs, he arrived in a state of starvation at the huge main railway station in Beijing. Here another new phenomenon met our eyes and feet as the entire huge main hall was a camping ground for peasant families who all intended to change to city life and "to make a lot of money". They were so densely packed together on their mats between their various bits of luggage, hens and kids, that we and our guide had difficulty finding a way out and finding a taxi to take us to the hotel.

We spent four days in Beijing, enjoying some of the delights reserved for the privileged guests of the Ministry of Health. We visited the Forbidden City for the second time (in 1978 the place was empty, now it was filled with visitors from all over China and Hongkong; not many Westerners), the wonderful "Blue" hills and their temples, the Summer Palace outside the town on its own large lake, the Lama temple, the Confucius temple, and the Behai pagoda and park. We did not venture beyond the ancient Tatar-District with its official buildings and museums. In Beijing, we were invited by all our friends to their homes, for instance to the home of Ambassador Yu Pei-Wen and his wife, Minister Ghu, and their daughter-in-law Zhu Ling (our pupil and now professor of hematology in Beijing). We were also invited to the small "imperial apartment" of another pupil, Liu Er-siang, and his wife, both professors at the Academy of Sciences. On this occasion other ex-pupils from Geneva such as Zhang Ziahong had prepared their best meal and brought it to this unique place, with its antique mahogany furniture, in our honour. Ch'En Wench'ieh brought us a huge copy of a black Tang horse, not thinking that we had to continue later on to Nanjing, Shanghai, Osaka and Taipei. But in the Middle Empire this did not really count - these were all manifestations of thanks to PAM and this huge town seemed just one family (which already counted 6 million people).

中 国 医 学 科 学 院

THE CHINESE ACADEMY OF MEDICAL SCIENCES

谨　　对

APPRECIATES AND RECOGNIZES

Dr. Peter A. Miescher

来 我 院 讲 学 表 示 感 谢

FOR THE VISIT AND ACADEMIC ACTIVITIES

中国医学科学院院长
PRESIDENT
CHINESE ACADEMY OF
MEDICAL SCIENCES

顾方舟

日 期：
DATE: March 10th, 1986

中 国 北 京
BEIJING, CHINA

Director:
Institute of Hematology,
BMU

Vice President:
Chinese Medical Assoc.

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sincerely yours

D.P. Lu

4.II.86 LU, Dao-pei

On 1st. March there will be a meeting at Beijing Medical University to confer formally the honorary professorship on you. This is really our honour and pride.

DISTINCTION CHINOISE
POUR LE PROFESSEUR P. MIESCHER

Le professeur Peter A. Miescher, de la Faculté de médecine de Genève, chef du Centre de transfusion sanguine, de la Division d'hématologie et du Laboratoire central d'hématologie, a été élevé au grade de professeur honoris causa de l'Université de Pékin. La cérémonie a eu lieu à Pékin le 1er mars 1986 en présence du professeur Qu Mianyu, président de l'Université. Dans son allocution, ce dernier a souligné les mérites du professeur Miescher, dont les travaux dans le domaine de l'immunologie clinique et de l'hématologie ont fortement influencé le développement de la médecine en Chine. Le professeur Miescher a ensuite donné une série de conférences à Pékin. Le 10 mars 1986, son activité au sein de l'Académie chinoise des sciences médicales a été honorée par un diplôme de distinction délivré par le président de cette institution, le professeur Gu Fang Chow.

ooo

Un service moderne d'hématologie sera mis sur pied prochainement à l'Hôpital universitaire de Pékin. A cette fin, une jeune doctoresse chinoise est venue compléter sa formation en hématologie à la Faculté de médecine de Genève, dans la division du professeur P. Miescher, grâce à la Fondation Lord Michelham of Hellingly. (Voir dernière édition, p. 10.)

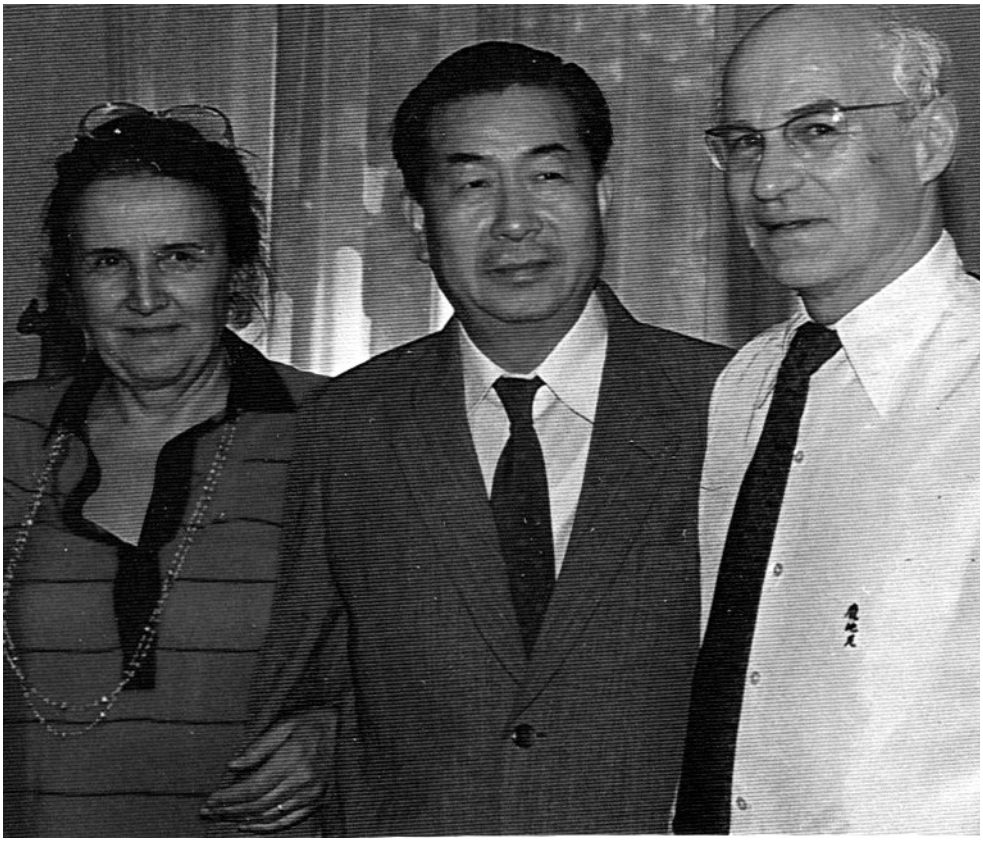
ZHOU LING

聘书

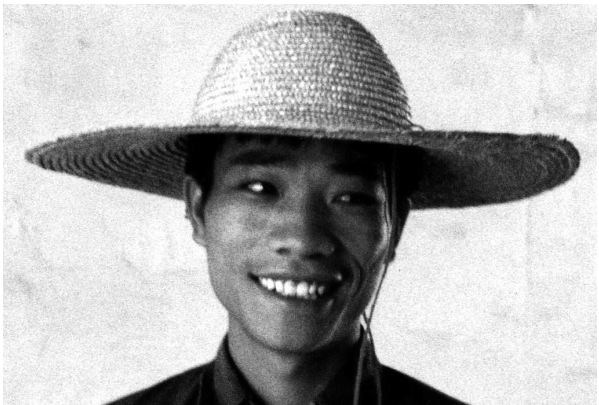
兹聘请米歇尔教授
Peter A. Miescher, M.D.
为我校名誉教授

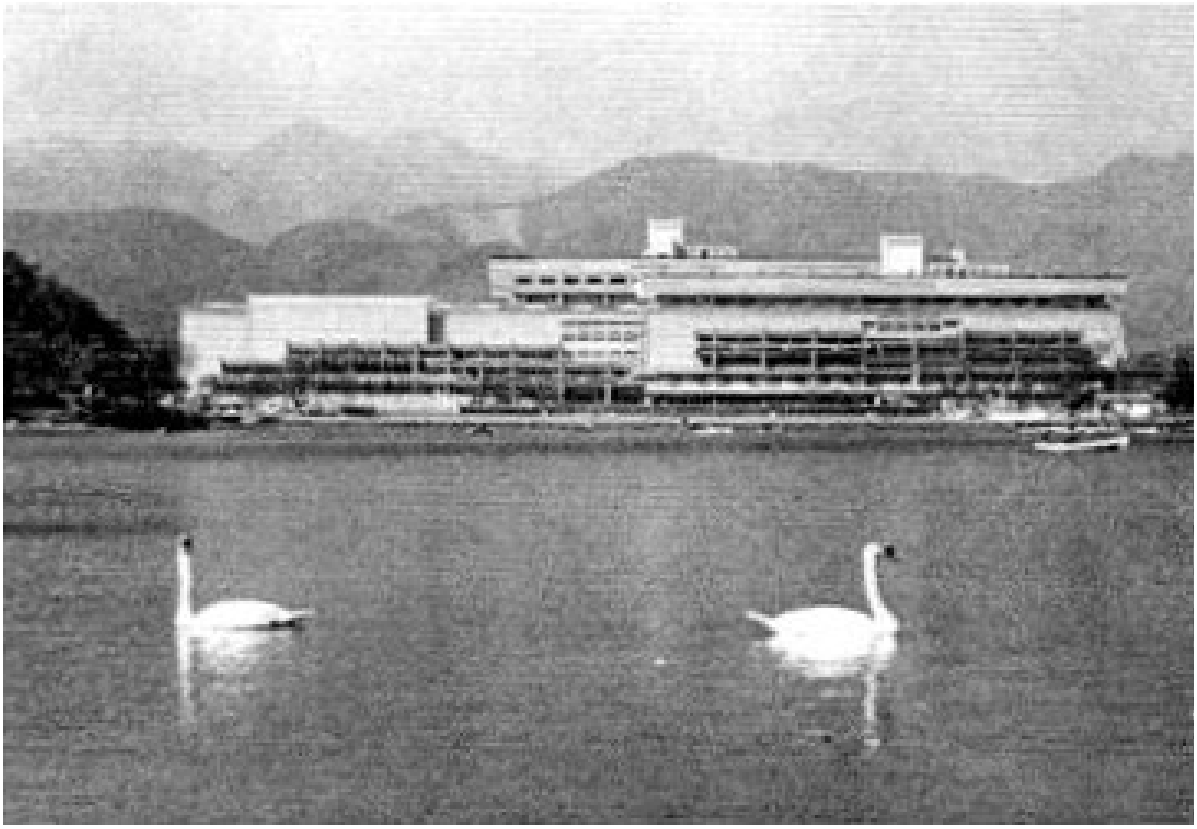
北京医科大学校长 [illegible]
1986年3月1日
聘字名第10号

CU Yue-li, the Minister of Health of the P.R. CHINA 1986, with P.A. and A. Miescher, Beijing.

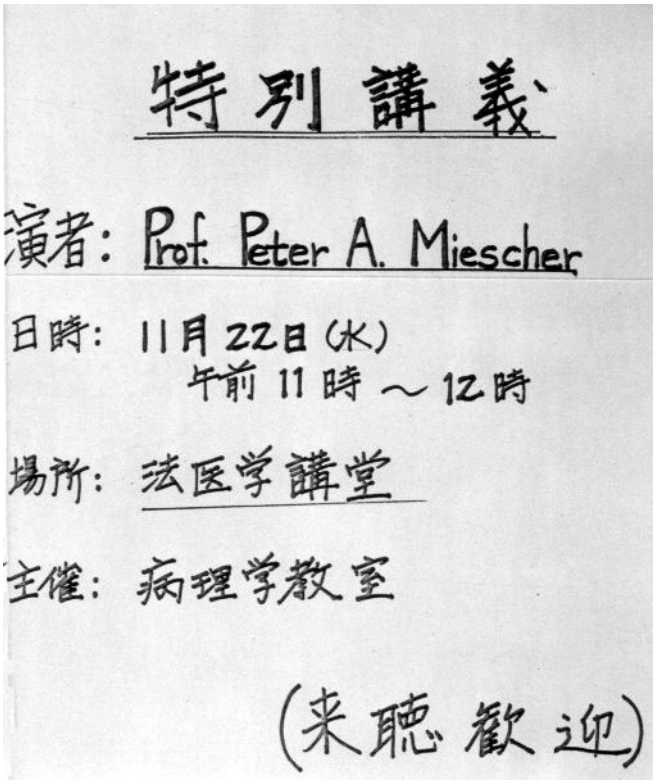


…with admirer from Geneva





Congress Center, Kyoto



特別講義

演者: Prof. Peter A. Miescher

日時: 11月22日(水)
午前11時～12時

場所: 法医学講堂

主催: 病理学教室

(来聴歓迎)

Peter with Professor Hiroshi Hamajima and collaborators

At 9 a.m. on Tuesday, PAM gave a lecture on the same topic to the medical staff at Kyoto University, followed by lunch at the university club, then sightseeing in Kyoto city, an evening visit to a Geisha house where PAM enthusiastically offered his Swiss-made wristwatch to a most charming and sad Geisha. On Wednesday, 11 May, in less than 3 hours with the "Hikari 264" we were in Tokyo. We spend a delightful evening at the Kabuki theatre.

In the afternoon of the next day PAM gave a lecture on RA for the doctors of the department of physical therapy at Tokyo university, followed by a huge dinner given by Sandoz. On Friday, 13 May, PAM gave a special lecture for the Sandoz staff.

Our last day was spent with our famous friend, Professor Tomio Tada, from the immunology department of the Tokyo university faculty of medicine, who had just been awarded a Japanese equivalent of the Nobel prize, presented by the emperor. We saw the difference immediately since he was wearing a suit (Western style) "of an immortal" instead of the hippy-wear of older times. We went with Tada and his down-to-earth wife to the Asaksa district to buy popular, handcrafted souvenirs. As we understood it, Tada identified himself with the yomono-aborigines of Japan. In the Ghinza district we bought many wonderful Japanese porcelains which were all sent to Geneva via trans-Siberian rail and which all arrived in one piece.

On Sunday, 15 May, we flew from Narita airport with Taiwan Air flight CX 451 to Taipei. The flight took 3 hours. On arrival, for the first time in Asia we had to queue for about an hour, since anybody could be a spy or other unwanted specimen on this troubled island. Waiting for us in the arrivals hall was the cousin of Huang You-peng, our collaborator from Changsha of imperial origin. At 09h00 next day, PAM was to lecture at the Veterans General Hospital (the best in Asia!) on "Concept and treatment of autoimmune diseases" followed by discussion, at 13h00 another lecture on "Myelodysplastic states: pathogenesis and evolution of disease", followed at 15h00 to 17h00 by bedside teaching with the splendid Professor Wang Soo-Ray as moderator. This was really squeezing the lemon - but PAM was in his element, his wife almost dead!

On Tuesday, 17 May, 08h00-11 h00: National Palace Museum then lunch with an antiques dealer at his home, where we acquired our best jade souvenir. 14h00-15h00: Municipal Art Museum. 16h00: departure for Taichung, dinner at Dr Peng's home. Next morning, return to Taipei and the Veterans General Hospital, briefing, grand rounds, lecture "New concept of pathogenesis and treatment of rheumatoid arthritis", followed by bedside teaching and discussion, dinner at the Grand Palace Hotel at 18h00, later Long-Hsan (= dragon mountain) temple and Hwa-His Street, the most authentic ancient Chinese scene we had seen so far. Taiwan is full of snakes and there were stands offering to young men fresh blood dripping from freshly sliced specimens. The smell of incense, the shrill voices, and the crowds of "home-sick" Chinese (i.e. the Taiwanese) buying silk goods, foodstuffs, shoes, anything - an unimaginable experience for us.
The next day we were in Hongkong and at 06h00 on Friday, 20 May, we arrived in Frankfurt with direct flight CX 289, then 3 hours later took a 70-minute Lufthansa flight to Geneva (at 65 one is very young indeed!).

湖南医学院
中华人民共和国、湖南、长沙
HUNAN MEDICAL COLLEGE
(NOW CHANGED TO HUNAN MEDICAL UNIVERSITY)

March 29, 1988

Professor P.A. Miescher
Division d'Hematologie
Hopital Cantonal
CH-1211 Geneve 4
Switzerland

Dear Prof. P.A. Miescher,

I am very glad to learn that you will visit some cities and give lectures this year in China.

We all know you are a famous heamatologist. You have been contributing to this field. And Dr. Guo, a staff of our university, have been at your laboratory to study for two years. Thank you for your enthusiastic direction, support and help to him. May I take advantage of the opportunity of your visiting China, to invite you to visit Changsha after you finish your visit to Chengdu. I hope it will be convenient for your wife and you to meet your old friends in Changsha, whom you met in 1979. We would like also to organize a short term--say a week--class with you as the chief lecturer, if it is convenient for you. As for the funds, the University will provide you with a single trip flight ticket from Changsha to Beijing or Shanghai as well as board and lodging for both of you during your stay in Changsha. I assure you my deep appreciation of your patronage.

I look forward to hearing from you.

With my best regards,

Sincerely yours,

Luo Jia-dian

Dr. Luo Jia-dian
President
Hunan Medical University

Changsha, Hunan, People's Republic of China
Telephone: Changsha 24411 Cable Address: Changsha 6829

Professor Peter A. Miescher

IN APPRECIATION OF

HIS CONTRIBUTION TO THE 1988 VGH TEACHING PROGRAM

TAIPEI, R.O.C., MAY 18,1988

Kwang-juei Lo.

KWANG-JUEI LO, M.D.

DIRECTOR

授予米歇尔博士华西医大内科荣誉教授仪式
Conferring Ceremony for P.A.Mischer As Honorary Professor of Medicine WCUMS
West China University of Medical Sciences
CHENGDU,Prov.of Sechuan,PRC.
1991,November 4

On Monday, 25 April 1988 we went by plane to Zhenzou and from there took the train to Luoyang, where we spent 3 nights. Luoyang is an industrial town which dates back to the time of the northern Chou (about 700 B.C.) and was also the capital at the time of the Tang dynasties. The famous Longmen caves from the 6' century B.C. with their hundreds of statues of Buddha (nearly as impressive as the Yunkang caves near Datung which we visited in 1979) were very much worth coming to see; in addition, PAM gave a talk at the medical college.

A further 5-hour train ride took us to Xuzhou. Incredibly, one complete street had been dug up: hundreds of terracotta statues had been discovered, about 60 cm high, in the old Han style, well protected from looters, some seemed intact, others broken. We spent the night there and continued the next day on to Nanjing, which means the "South-Capital". It was lovely spring weather and we stayed 4 nights at the wonderful Jingling Hotel where the tall, elegant waitresses in their red velvet gowns were most impressive. The professors at Nanjing hospital were all female, lovely temperaments and competent enough to enjoy PAM's conference and the subsequent rounds of different wards. Two days later, our colleagues wanted to show us Yangchou, the ancient center of Zen Buddhism, about 100 km down the other side of the Yangtze river. One wonderful ancient temple seemed to have much in common with Taoist roots and the place was filled with Japanese Zen adepts. On our return to Nanjing, we wanted to give the chauffeur a tip of 100 yuan, but one of the professors quickly intervened, "Stop! That is what we earn in a year - taxi drivers are rich people."

Again, a 6-hour train journey to Shanghai, where we refound old friends: Professors Pan Shuipeng (hematologist), and Chen Shun-le (rheumatologist) at the Ren Ji Hospital; Professor Wang Zhenyi at the Shanghai 2' Medical University, and Professor Wang Yifei, director of the WHO Steering Committee on Contraceptive Vaccines, all interested in having PAM's opinion on various topics. We nevertheless found time to visit the wonderful collections at the archeological museum and to buy some splendid embroideries from around 1860, intact and impossible to find today at any price. For example, a 4-metre long silk embroidery on red wool, showing the 8 immortals with Si Wang Mu, the queen mother of the western sky.

Very recently (in 2005), our friend Hu Chingli, ex-assistant director-general of WHO, Geneva, and from Shanghai, wrote to say that we could not imagine how much Shanghai has changed in 17 years, with over 3,000 skyscrapers, new towns, high-speed train to the new airport, etc., etc., with only the old Wangpoo river - as dirty as ever - flowing quietly alongside the Yangtze down to the China Sea.

Saturday, 7 May 1988, we took flight CA 915 from Shanghai's old airport to Osaka, Japan, arriving at noon after a calm, 3-hour flight, and were picked up by our ex-collaborators from the Geneva WHO unit, Drs Yoshida and Sekida, both now in high positions in their respective hospitals. The next morning, we took the super express train "Hikari no. 344" which, in 16 minutes, brought us to Kyoto. Here, our old friend, Professor Hamajima, immediately took us on a "Nara full-day tour", visiting the oldest Horyu-ji shrine of Japanese Buddhism (this religion was brought over from Korea in the 7`h century AD, over 1'000 years after the birth of Siddhartha Gautama). In the Todai-ji temple, the 16-metre bronze statue of Buddha and the wooden guardians, the temple itself, all in their original splendour, over 1,200 years old, never damaged by fire or enemies, are worth the trip. In the afternoon, we visited the large city park, the imperial museum, etc. Later in the day, PAM gave a lecture to the students of the Kyoto Prefectural University of Medicine on "mechanisms and treatment of autoimmune diseases", followed by rounds at the Amagasaki Prefectural Hospital with Dr Yoshida.

7.8 Seventh visit to China (1991)

At this point, we would like to finish our Asia chapter. In 1991, PAM accepted to fly to Sechuan in the PRC once more as he was to be honoured at the University of Chengdu. This Asia trip had to be combined with a promised visit to Philadelphia to celebrate PAM's association with Seminars in Hematology with the publisher and editorial team. On Sunday, 20 October, we were delighted to have a visit from our daughter, then assistant professor of psychiatry at NYU. As her work called her back to New York, we just had time to realize that she enjoyed her aging parents even though we had not seen her since 1989 in Geneva. She loved her job and her life in New York, our old hometown of more than 20 years before. The Seminars meeting was the next day but beforehand we could not stop ourselves from visiting the oriental collections in the museum: the far-east fever was real. We had dinner with our friends Professor Ernest Jaffè and his wife, Jane, and Mrs Livia Venturi from WB Saunders, the publishing company.

On 22 October, we were invited to the NIH in Bethesda where PAM gave a seminar. That evening we had dinner at the home of the head of the infectious diseases division, where the Steinbergs showed us the paintings they had done themselves. It was really wonderful. On the 23rd, we flew to San Francisco, where we stayed until the 26*th*. We met up with our friend from Syntex, Tony Alison. We also visited the museum of oriental art, where we were able to much better appreciate what we had seen during the hurried sightseeing tours in between PAM's conferences in Asia.

On 1 November we landed in Hongkong, the next day in Guangzhou (Canton). On 3 November, we finally got validated tickets at this airport for a flight to Chengdu; the race for plane seats had gone amok. On 4 November (the birthday of PAM's late father, Guido), PAM was handed the document that named him "Honorary Professor of Medicine at the West China University of Medical Sciences" (see photo of the memorable moment). PAM then gave an address to thank the authorities responsible for conferring this distinction upon him, by their recognition of all he had done for their medical school in promoting knowledge and improving the teaching, as well as inviting staff members to visit the Geneva institutes. (Indeed, Deng Chang-an, professor of internal medicine at WUMS, later stayed at our Geneva home for one week, and visited our hospital laboratories, WHO, Berne university and Sandoz in Basle; Tang Huayang worked with us for several years in Geneva.)

Three days were quickly filled with conferences, ward rounds and seminars in the university clinics. We then prepared to travel eastwards, first visiting by rail above Youtingpo a most impressive sequence of huge cliff carvings illustrating the Buddhist "bible for the poor", called Dazu (= big foot): over hundreds of metres, the teachings of Buddha were carved out of the sandstone slopes of the western bank of a small river, with life size figures (these carvings were also often painted). A small path underneath incited visitors to admire "filial piety, the training of buffaloes, preaching to the old and sick, as well as helping the disabled ..", sculptures of the Tang or Southern Song times. It was raining slightly and there were nearly no other visitors except Tang Huayang and a girl from the tourist office. We then had to hurry to catch the train to Chongqing, about a 4-hour trip, where we spent the night. In the early hours of the next morning, Tang took us to the airport, and we caught the direct flight to Hongkong. The next day, after 13 hours traveling, we reached Zurich and finally Geneva.
This was definitely our last trip to the Far East even though the journey had taken just half the time it had taken in 1978 when we first went to Hongkong. Our duty was done, the Ministry of Health had offered this unique opportunity to us and to the new generation of Chinese physicians to get in touch, and to both sides the possibility to open their minds. Thirteen unforgettable years had passed. Even now, more than 25 years later, one part of our lives remains Chinese.

7.9 International Exchanges

Other trips during this period took Peter time and again to the USA: 1980, 1982, and 1986 to Houston, as Blaffer visiting professor at the M.D. Anderson Clinic. In 1984, Peter was offered the chair of internal medicine there following the departure of Professor Conrad.

In 1980, we were in California visiting La Jolla and San Diego where we attended the 60*th* birthday party of Baruj Benacerraf and visited Dr Jonas Salk. Peter gave lectures in San Diego and Los Angeles. Professor Roy Walford was interested in the aging process and had found that lowering the body temperature let his hashish-addicted mice grow significantly older than the control animals. This was why we ended that day in "Little Venice", a hippy seaside part of the town, in the company of a dozen or so joint-smoking professors from various places, invited to have a "high" with Roy, lying on the ground, passing the "joints" around. With the excuse of "having forgotten" an important overseas call, we fled into the dark night, ending up on the highway and saving ourselves by a risky hitch-hike manoeuvre back to the hotel!

In 1984, an interesting teaching trip took us to Bulgaria to the towns of Sofia and Varna, where our guide was a very intelligent doctor who spoke French and German and who translated Peter's lectures into Russian (the Iron Curtain still existed and Bulgaria was isolated in the eastern block). All went well, but soon after our return to Geneva, we were visited by the national security police from Berne, who accused Peter of violating the law by telling valuable secrets to enemies of the West! From our passports they thought we had been in Russia since no-one in Berne could read Cyrillic letters.

In Geneva, Paul-Henri Lambert, the WHO professor of experimental immunology (a post paid by the Annette Kade Foundation created by Peter Miescher in 1968), was by this time known worldwide for his excellent training center. Visiting scientists included Dodson Creighton from the USA (for several years in the 70s), Dr A. Bankhurst from Australia, and Professor Karl-Hermann Meyer zum Bueschenfelde from Mainz who spent his sabbatical leave with us working on immune hepatitis problems (189).

In 1981, the first Chinese visiting scientist arrived at the Geneva-WHO center. This was Professor Liu Er-siang, a malaria specialist from the Chinese Academy of Medical Sciences in Beijing, who stayed for two years. Malaria had become more and more widespread in China, even in the northern regions (they had started to cultivate rice not far south of Beijing to be able to feed the growing population, but unfortunately the Anopheles mosquitoes followed too!). In our laboratories (mainly with Dr Luc Perrin), we studied the possibilities of developing a malaria vaccine.

In 1965 at New York University, we already had a Japanese research fellow, Dr H. Nakashima (136). More that 10 years later, Dr Shozo Izui became the first Japanese fellow in Geneva. Shozo Izui made his career in Geneva and in 1985 was appointed professor of experimental pathology at Geneva University. This is just to show that collaboration with the Far East started before our many conference tours to Japan and China between 1978 and 1991. In 1981, a whole family came from Kyoto (sent by Professor Yoshihiro Hamashima of Kyoto University) to Geneva: Haruyoshi and Michiko Yoshida, both medical doctors, with their three daughters, a fourth being born in Geneva. They worked on immune complexes in our WHO group from 1981 to 1983.

In spring 1982, PAM was invited by Professor Miamoto, director of the University of Tokyo School of Medicine and Physical Therapy, to give a lecture on rheumatoid arthritis. At the University we also met Professor Tomio Tada, later to become our friend, from the Department of Immunology, and very many others, some of whom had done part of their medical studies in the USA and spoke better English than our Chinese friends. Many of them came to Geneva to visit the WHO laboratory, which in the meantime had gained a reputation for its short training courses for medical doctors from Asia and Africa, and also from nearer places such as Italy (with future professors such as D'Amelio, Valesini, etc.).

8. Transition Geneva – Italy

We left Geneva, having sold our house there, when I retired from the University in September 1994 (after 26 years). We have, however, kept in touch with ex-colleagues and associates. Jean Ringrose, for instance, who helped prepare and edit all my scientific papers and presentations, still handles the editorial work in connection with “Seminars in Immunopathology”, which I co-edit with Shozo lzui (Geneva) and, since 2001, with Eyal Raz (La Jolla, CA), who succeeded Hans Spiegelberg as co-chief editor.

How did we come to choose to retire to Italy? A number of contacts had gradually been established over the years. Dr Genesio Balestrieri from the Brescia community hospital (Ospedali Civili) did his training in immunology at our WHO Research and Training Unit. He subsequently remained in contact with Geneva. He organized annual clinical courses during which difficult cases were presented to me. All physicians at the Brescia hospital who were interested in immunopathology participated at these courses.

In 1987, a family from Parma came to Geneva with their child who was suffering from a severe transitional form of SLE and RA. A complex drug combination therapy was set up at the attention of the child's pediatrician, Dr Laura Zavota of the pediatric outpatient department at Parma University Hospital. As the boy, Emanuele, did not improve sufficiently on this therapy, Dr Zavota suggested adding i.v. gammaglobulin, which proved very effective. Subsequently, Professor Giorgio Ghirardini, who had given Dr Zavota (his assistant) complete freedom to follow my school of treatment, asked me to be consultant to his department and to come to Parma regularly for clinical rounds. At each visit in Parma, I gave a conference on drug combination therapy.

Our activity came to the attention of the ophthalmologist, Jelka Orsoni, who soon joined the "Autoimmune Club of Parma". Indeed, chronic intra-ocular diseases often turned out to be systemic affections, involving the spleen. Drug combination therapy entered the field of ophthalmology. Thus, Parma soon became a center for the treatment of uveitis, a group of diseases mostly considered to be local conditions but which are often the expression of a systemic affection.

Otolaryngology, in particular Dr Piazza, also joined the “Parma Autoimmune Club”. For example, the Cogan syndrome turned out to be a systemic disease with splenomegaly. Neither ophthalmologists nor ORL-specialists had ever thought to investigate the spleen before!

In June 1985, I was asked to see urgently a patient from the Republic of San Marino. As I was scheduled to be in Brescia the next day, it was arranged that I should see him there. The patient, Filippo Vicini, was brought to

me on a stretcher, having been transported to Brescia by ambulance from San Marino. He had to be hospitalized immediately for treatment of aplastic anemia (hemoglobin was 3 g/dI, the bone marrow appeared "empty" on aspiration). Under immunosuppressive treatment, Mr Vicini gradually recovered from the aplastic anemia remaining up to this day under immunosuppressive treatment. My collaboration with San Marino started with this patient.

In subsequent years (from 1993 to 2000), I visited San Marino annually as clinical chief consultant to the newly founded “Center for the Treatment of Autoimmune Diseases”, meeting with the house-staff of the San Marino State Hospital and the head of the department of medicine, Dr Gian Carlo Ghironzi.

Several patients who consulted me in Geneva were from the Ligurian coast. One Italian patient with advanced RA was also being followed at the Princess Grace Hospital in Monaco by the orthopedist, Dr Philippe Ballerio, who learned through this patient about our new therapeutic approach to RA. Dr Ballerio became particularly upset when his RA patients had a severe inflammatory reaction in a joint he had operated. He asked me to give a talk at the hospital in Monaco about the treatment of RA. This I did, stressing the necessity to prevent post operative inflammatory reactions, so as not to compromise the success of surgery (i.v. injection of 15 mg MTX together with 125 mg Solu-Medrol administered 10 days after the operation). In this way, I became consultant to the orthopedic division of the Princess Grace Hospital in Monaco, where we acquired a small flat in 1987.

With my Italian professional contacts during all these years, it is understandable that we set up a temporary home in Urbino, just 50 km from San Marino and 250 km from Rome. Our choice proved to be ideal since physicians from all over Italy could consult me.

It should perhaps be mentioned that I have “Italian roots”, since some of my ancestors had emigrated from Switzerland to Naples over 150 years ago. My father was actually born in Naples in 1887, but had to leave Naples to go and live in Basle at the age of 9 due to the sudden death of his father. Later in life, he returned nearly every year to Italy.

Now, at nearly 82 years of age, I am still busy as consultant, thanks to my Italian colleagues and their patients. My nearest academic center is Rome with the Sant Andrea Hospital of La Sapienza University, where I am "honorary consultant" to the Division of Immunology, headed by Professor Raffaele D'Amelio. D'Amelio actually did his immunology training at the WHO Research and Training Center at my former division of hematology in Geneva. One of his close collaborators is Professor Bruno Laganà, a gifted physician and scientist. With Laganà, in 2003, I introduced a new echographic method, using a "linear echo probe", for the exact measurement of the spleen, of primary importance for monitoring disease activity in most collagen diseases (272).

I also remain in close contact with the Parma group and with Brescia, where my pupil, Dr Maria Rosa Metelli, follows a few hundred patients suffering from autoimmune diseases. In Monaco, Dr Stéphane Léandri is another gifted physician and pupil.

IL CONSIGLIO GRANDE E GENERALE
della Serenissima Repubblica di San Marino

Per Decreto del Gran Magistero dell'Ordine Equestre di Sant'Agata delli 2 Marzo 1984

HA NOMINATO

il Prof Peter Anton Wiescher residente a Ginarra

Commendatore

...ota con facoltà di fregiarsi della decorazione stabilita dagli Statuti pel grado equestre conferito Gli

Noi Capitani Reggenti

ORDINIAMO

...vito il presente Documento munito ...o e firmato di Nostra mano

...Capitani Reggenti

1985-1993 Consultant at the Istituto per la Sicurezza sociale REPUBBLICA DI SAN MARINO

1993-2000 Consultant of the Founder and Chief Consultant of the CENTRE FOR THE TREATMENT OF AUTOIMMUNE DISEASES and creating a FOUNDATION for scientific activities

FONDAZIONE SAMMARINESE MALATTIE AUTOIMMUNI
ISTITUTO PER LA SICUREZZA SOCIALE
Prof. Peter Wiescher
Per le grandi doti umane e professionali

Il Segretario di Stato per gli Affari Esteri

AZIENDA OSPEDALIERA
SANT' ANDREA
UNIVERSITÁ DI ROMA "LA SAPIENZA"
SECONDA FACOLTÁ
DI MEDICINA E CHIRURGIA

U.O.C. AFFARI GENERALI

Roma, 22/07/2004

Prot.AA.GG. n. 1726

Al Prof. Peter A. Miescher
U.O.C. di Allergologia, Immunologia Clinica e Reumatologia

Al Prof. Raffaele D'Amelio
U.O.C. di Allergologia, Immunologia Clinica e Reumatologia

E p.c. Al Direttore Sanitario
Dott.ssa Maria Paola Corradi

OGGETTO: **Incarico di consulenza onorifica al prof Peter A. Miescher**

Si comunica che con deliberazione n. 812 del 15/07/2004 è stato conferito alla S.V. un incarico di consulenza onorifica nell'ambito dell' U.O.C. di Allergologia Immunologia Clinica e Reumatologia dell'Azienda Ospedaliera Sant'Andrea.

Come citato nella suddetta delibera, tale consulenza onorifica presupporrà, oltre che un rapporto telefonico per casi particolarmente complessi, un impegno configurabile in due o tre settimane all'anno, presso l'Azienda Ospedaliera Sant'Andrea, per esaminare direttamente i casi afferenti all'U.O.C. di Allergologia, Immunologia Clinica e Reumatologia.
Tale periodo sarà concordato con il Prof. Raffaele D'Amelio, Responsabile della suddetta U.O.C. di Allergologia.

Si fa presente altresì che il Prof. Raffaele D'Amelio è stato individuato quale responsabile dello svolgimento di tale consulenza onorifica da svolgersi di concerto con la Direzione Sanitaria dell'Azienda Ospedaliera Sant'Andrea.

Il Responsabile U.O.C. Affari Generali
(dr.ssa Rosa D'Arca)

AA.GG./RDA/SP

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MONACO, residence since 1988

9. EPILOGUE

The modern concept of a biological approach to the practice of medicine was introduced 100 years ago by Claude Bernard: "The physician should never be doctrinal, he exercises criticism and expresses doubts, avoids fixed ideas and continuously maintains his freedom of thought".

During the last 50 years, clinical immunology has demonstrated that Claude Bernard'sadvice is still valid. How many times have we had to change our concept of basic immunology to arrive at today's understanding of the complexity of the human immune response?

The task of the modern physician is not an easy one in regard to autoimmune diseases, as they differ from patient to patient and many factors influence their course. The physician cannot enter a diagnosis into his computer and receive in return a fixed therapeutic protocol. The variations in the genetic background alone are such that he has to accept the fact that every patient has his own autoimmune disorder. If officially medicine recognizes some 40 different autoimmune diseaseentities, in reality there are many more. In addition, we have had to learn that we are not dealing with rare human pathologies, but effectively with diseases affecting more than 5% of the population.

My own biographical notes may reflect some of the development over the past 50 years in this fascinating field of human pathology. When dealing with autoimmune diseases the clinician needs a thorough knowledge of the basic immune phenomena if he is to provide the patient with a "treatment based on mechanisms of disease". No doctrinal protocol will be successful; on the contrary, great flexibility is required to adjust treatment to the patient's ever-changing physiopathological status.

"La medécine empirique et la médecine expérimentale, loin d'être incompatibles, doivent, au contraire, être réunies intimement. " (Claude Bemard).

P.A. Miescher
Urbino, May 2005

10. Extract from: Hematology, the blossoming of a science: a story of inspiration and effort. Maxwell M. Wintrobe, 1985 (pp 432-433)

A noted immunopathologist in Switzerland is Peter A. Miescher (1923-) who was born in Zurich of a family with physicians on both sides. His great-grandfather was Professor of Pathology in Basel and his great-grandmother was the sister of Wilhelm His, a well-known physiologist whose son of the same name discovered the cardiac bundle branch named after him. One of his ancestors had discovered the nucleic acids and also demonstrated the relationship between altitude and hemoglobin concentration. Peter Miescher graduated in medicine at Zurich and became interested in immunology because, it seems, the subject had been taught so badly that he was forced to read intensively on the subject. Following graduation he worked in the Department of Experimental Pharmacology of the Ciba Company in Basel, interned in pediatrics and internal medicine in Davos and in Lausanne from 1951 to 1954, and was chief resident in medicine at the University of Basel for the next five years.

As a first-year resident in internal medicine, Miescher encountered a patient with idiopathic thrombocytopenic purpura (ITP), a condition that at that time was considered by some to be due to the inhibitory action of a splenic factor on the bone marrow. His immunologic interest led him to investigate the action of the hypothetical factor on rabbits, and thus he found that it was an immunoglobulin that could be specifically absorbed onto human platelets. It produced in the rabbit an acute drop in the platelet count, with lethal effect. The serum lost its platelet activity when absorbed with human platelets or when the rabbit was protected with a strong antihistaminic drug. He concluded that the lethal shock to the animal was due to the sudden release of serotonin from platelets upon their destruction. Interestingly, splenectomy protected the rabbit. He then studied Sedormid-induced thrombocytopenia and showed that the offending agent could be recognized as a soluble immune complex. In 1953, he described a leuko-agglutinin that developed following blood transfusion and was shown to be of isoantibody nature.

While Miescher was a resident in Lausanne, Hargraves described the LE cell phenomenon, and Miescher began to direct his attention to this topic, one on which he and his associates continue to work. He demonstrated that antibodies to cell nuclei can produce phagocytic phenomena that resemble the LE cell, and he then showed that the LE cell factor could be absorbed onto isolated cell nuclei but not by intact leukocytes. This led to the finding that the LE cell phenomenon is due to the action of antinuclear antibodies that react with nuclei once the cytoplasm has been damaged. He also showed that drugs can lead to LE cell formation as an expression of drug allergy. Investigation of the antigenic constituents of the cell nucleus led to discovery of antibodies against nucleoprotein and DNA. These discoveries were followed by similar observations at the Pasteur Institute in Paris by Maxime Seligmann and at the Rockefeller Institute by Halstead Holman, who was working on the LE cell phenomenon in Henry Kunkel's department.

Peter Miescher's work was accomplished in spite of limited facilities and limited funds; nevertheless, his research on immunopathology soon became well known. Invited to serve as Visiting Professor by New York University, he remained ten years, established a Hematology Division in the Department of Medicine and investigated, among other topics, the role of complement in the elimination of antibody-coated red cells. In 1969 he was appointed Professor of Hematology and Chief of the Blood Bank at the University of Geneva, and there he has remained. His research continues in the area of the interface of immunologic reactions and the hematopoietic system, but also has included studies on the mechanism of vascular purpura, chronic myelomonocytic leukemia, primary acquired sideroblastic anemia, and "primary acquired refractory anemia". The latter conditions he regards as the result of a somatic mutation and consequently representative of a monoclonal disorder susceptible to additional somatic mutations such as the development of leukemia. While thus continuing the tradition of his forebears, Peter Miescher also finds time for his interest in the arts, especially music, and is a fine cellist himself.

11. Ancestors

Peter Anton Miescher (1923) was most certainly never told (he found out for himself) that some of his forebears were famous scientists in the field of medicine. It could be that the young dreamer was not interested in identifying the characters in photos hanging in the family homes. In any case, it was in line with the protestant and puritan way of life of old Basle people. Genetics may be the main key to why, within four generations, there was an accumulation of outstanding scientists and physicians. In addition, the authority of the elders was admired and respected, their example followed.

Genetic talent accumulation very probably started with the marriage in 1844 of Friedrich Miescher (1811) with Charlotte Antonie His (1819). The name Miescher is connected with four generations of medical scientists; the name His was made famous by the younger brother of Antonie, Wilhelm His senior (1831), and his son Wilhelm His the younger (1863). The His clan belonged to the "Basle aristocracy", if such a thing existed, called locally "the paste" (= der Teig). See photos.

Let us start with the first of the four Mieschers, born nearly 200 years ago

Friedrich Miescher-His, born in 1811 in Walkringen (Berne), started his studies at the Bern Academy in 1832 and, having completed the basic education in medicine, he had the opportunity to continue his studies at the newly-opened Wilhelm von Humboldt University in Berlin. There he became fascinated by the lectures in physiology given by Johannes Peter Muller, the founder of modern physiology. Friedrich Miescher remained in Berlin for three years and graduated there, his main scientific paper being - in Latin - "De inflammatione ossium eorumque anatome generali". A renowned scientist already, he returned home at the age of 25. In 1837 in Basle, he obtained the title of Ordinarius of Physiology and General Pathology but, lacking students, he joined the Paris school of medicine where Magendie, the teacher of Claude Bernard, greatly influenced his future career. From the "evolution of bones", he turned to parasitology. His name remains associated with the "Sarcocystis miescheriana" – intramuscular tubes, formed by parasites, in mice as well as in other animals, also recently even described in man. His main merit was in establishing modern scientific disciplines at the University of Basle. In addition, he sang very well and played the lute. When he retired from the academic world, he practiced gynaecology and obstetrics. He died in 1887, much beloved, at the age of 76. A beautiful oil painting of him hangs in the Basle museum. Antonie, besides raising five gifted sons, is known for her scientific drawings illustrating the works of Friedrich. She died in 1896.

Wilhelm His Senior, born in Basle in 1831, the younger brother of Antonie Miescher-His. Studied in Basle, Berne, Berlin, Wurzburg, Prague, Vienna and Paris. One of his teachers was Rudolf Virchow who had a great influence on him. At 26, he was named Ordinarius of anatomy and physiology at the University of Basle. Fifteen years later he was appointed to the prestigious post of Professor of Anatomy at Leipzig University (1872). In the years 1870-1890 no other faculty in Germany had a higher number of renowned scientists and leading academicians. He planned and designed the new anatomical institute which opened in 1875. His main work is considered to be his precise history of the evolution of the central nervous system as well as the neuroblast theory. He died in 1904, the same year that he created in Amsterdam a central institute to coordinate the brain research being carried out in various establishments. He contributed in important ways to his specific field of interest and to the renown of the medical faculty in Leipzig.

His son, ***Wilhelm His Junior,*** born in Basle in 1863, a young cousin of ***Johannes Friedrich Miescher.*** Both born in Basle and "genetically" related, both of them most brilliant scientists, they had not met or influenced each other's career. Wilhelm His Junior died 29 years after Johannes Friedrich Miescher. His Junior studied medicine in Geneva, Leipzig, Bern and Strasbourg where, in 1887 he discovered the body's ability to methylate organic compounds. In 1888 he passed his final exams in medicine. In 1889, he was appointed Assistant in Leipzig, and in 1895 was nominated extraordinary Professor of Medicine. From 1902 to 1906 he worked as Ordinarius in Basle. In 1906 he moved to Gottingen and in 1907 was offered the prestigious chair of Internal Medicine in Berlin and was made Director of the first Medical Clinic (the "Charité"). In 1918 he was made Dean of the Medical Faculty and in 1928 became Rector of Berlin University. He had a brilliant career due to his excellent medical expertise, mainly as a cardiologist. In 1893, he discovered the specialized muscle fibres, now known as the Bundle of His, running along the muscular partition between the left and right chambers of the heart. He was one of the first to recognize that the heartbeat has its origin in the individual cells of the heart muscle. The history of medicine was another of his great interests; the arts also - he painted and played music. He died at the age of 71 and was buried in the town of his ancestors, Basle.

Johannes Friedrich Miescher (1844-1895), the first child of Friedrich and Antonie Miescher is known now as "the man who discovered DNA" since, long before Watson and Crick, he had isolated, analyzed and recognized DNA as a special macromolecule in 1869! Its unique physiological importance has increased in modern times, more than 100 years after its isolation. Friedrich called the substance he had isolated "nuclein". Friedrich II, as we call him, studied medicine in Basle, where his father and his uncle, Wilhelm His, were professors of pathology and anatomy at the university. As a young student, he partially lost his hearing due to a severe attack of typhoid fever. During convalescence, he had frequent discussions with his uncle Wilhelm, who lived in the same house, about his future in medicine. At that time Wilhelm His was working on the development of the foetus. Intrigued by prevailing ignorance about the composition of the cell nucleus which is in constant movement during cell divisions, he suggested that his talented nephew should focus on the biochemistry of the cell nucleus as a research topic at the institute of his friend, Hoppe Seyler. So, young Friedrich went to Tubingen after graduating in 1868 to work at the Institute of Physiological Chemistry. In 1871, he was appointed Professor of Physiology at Basle University. The material from which he isolated cell nuclear material was pus in Tubingen and salmon sperm in Basle (a century ago, the Rhine river, clean at that time, was famous for its salmon). His other preoccupations at that time were the bad nutritional status of the rural population and the low standards of food given to prisoners. He also discovered that it is the carbon dioxide concentration, rather than the oxygen concentration, in the blood, that regulates breathing. He died at the age of 51 from tuberculosis.

Friedrich and Antonie Miescher-His
with Johannes Friedrich

Johannes Friedrich Miescher
(1844-95)

Wihelm His sen.

Short Biography

- born in Basel on 09 July 1831
- studied in Basel, Bern, Berlin, Würzburg, Prague, and Vienna
- 1854 wrote his thesis
- 1856 wrote his MD habilitation[1] at Basel University
- 1857 appointed Fellow Professor [2] of anatomy and physiology at Basel University
- 1872 appointed Fellow Professor [2] of anatomy at Leipzig University
- 1875 the newly built anatomical institute in Liebigstrasse was opened; His was involved in its planning and design
- he is regarded as *"founder of an exact history of the development of the central nervous system"* as well as the neuroblast theory
- he proved that the mortal remains located in St Tom's Church are most likely those of composer Johann Sebastian Bach; he also helped sculptor Carl Seffner to create a possibly authentic monument to him which still stands in front of St Tom's (Thomaskirche)
- died on 01 May 1904

Wilhelm His der Jüngere

1863 - 1934

The body's ability to methylate organic compounds was discovered by German physician Wihelm His in 1887, when he isolated N-methyl pyridinium hydroxyde from the urine of dogs dosed with pyridine acetate. He studied metabolism with Schmiedeberg in Strasburg and went on to become director of the first medical clinic in Berlin. A musician and painter, His also pioneered studies in cardiac conduction and campaigned to promote disclosure of the composition of proprietary drugs.

Wilhelm His was born in Basel, Switzerland in 1863. The Swiss cardiologist discovered (1893) the specialized muscle fibres (known as the bundle of His) running along the muscular partition between the left and right chambers of the heart. He found that these fibres help communicate a sinus rhythm of contraction to all parts of the heart. A professor of medicine at the University of Berlin (1907-1926), His was one of the first to recognized that the heartbeat has its origin the individual cells of heart muscle.

Marietta Berner and

Max Eduard Miescher (1846-1891)

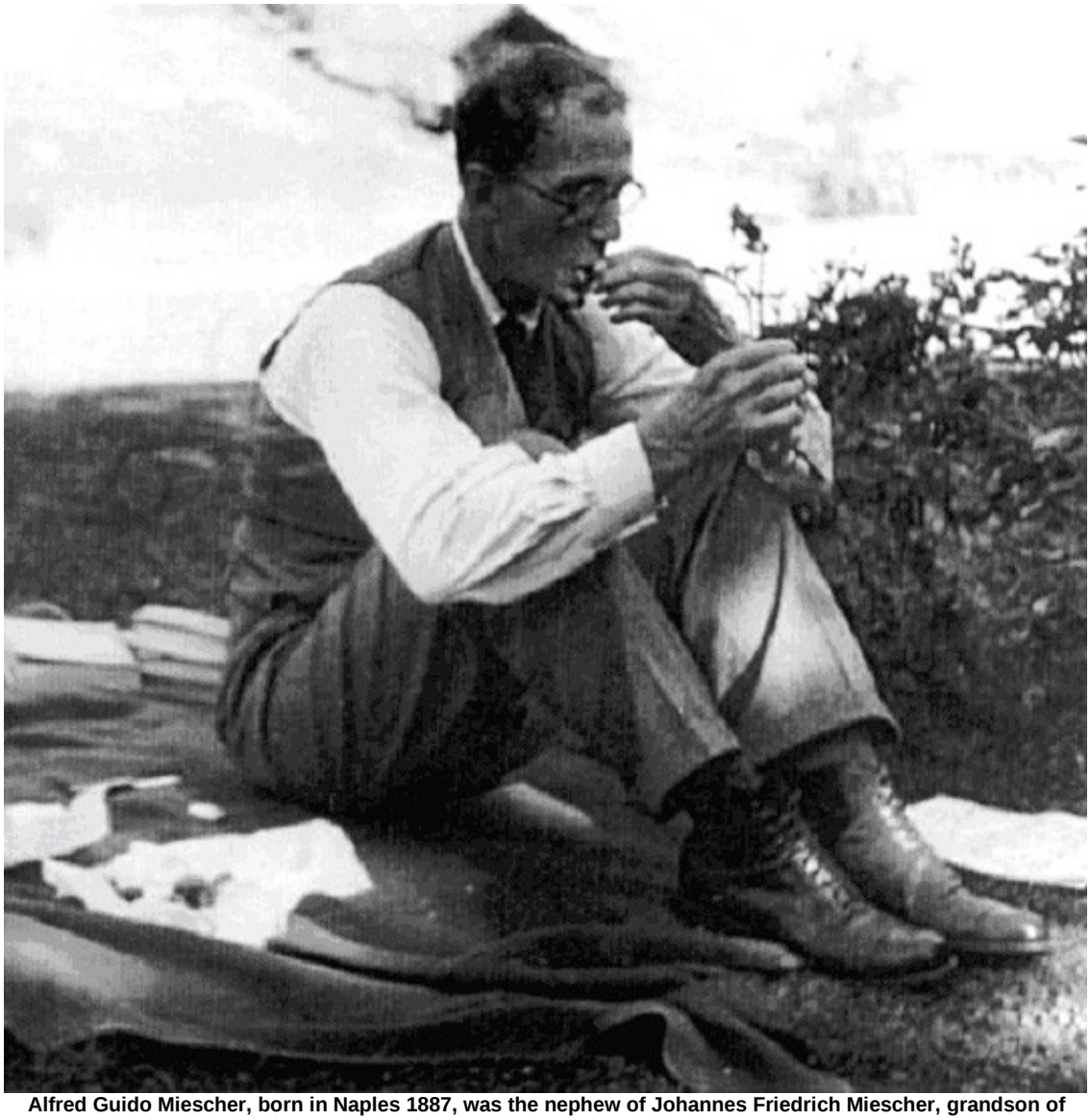
Their sons: Max, the elder, and the younger

Alfred Guido Miescher, born 1887 in Naples,

Later, 1896, in Basle. Father of Peter A

+


Miescher - Berner
1885
R. FERRETTI
NAPOLI
CHIATAMONE 25



Alfred Guido Miescher, born in Naples 1887, was the nephew of Johannes Friedrich Miescher, grandson of Friedrich Miescher-His and father of Peter Anton Miescher. He died in Zurich 1961.

Alfred Guido Miescher (1887-1961) was the nephew of J. Friedrich Miescher, grandson of Friedrich Miescher-His and the father of Peter Anton Miescher. He was an Italian-born Swiss dermatologist, born in Naples and died in Zurich. When he was 9, his father died suddenly of tubercolous meningitis. Following the death of his father, Max Eduard (1846-1896), he returned with his mother, Marietta Miescher-Berner (1860-1940, daughter of a successful industrialist of Swiss origin who, as a young emigrant, had created several industrial companies in Naples and other parts of Italy) and two brothers to Basle. After the gymnasium, Guido started to study engineering at the Swiss Federal Institute of Technology in Zurich but then went on to study medicine in Basle, Zurich and Munich, passing the final examination in Basle in 1913. In 1916 he followed his teacher, Professor Bruno Bloch (1878-1933) to the Dermatological Institute in Zurich. Guido Miescher graduated in dermatology and dermatological radiotherapy with a thesis on chromatophores. In 1928, he obtained the title of "Titularprofessor", from 1942-1944 was Dean of the medical faculty, and from 1948-1952 was President of the Swiss Academy of Medical Sciences. About five syndromes are called after Guido Miescher. He was a pioneer in the radiotherapy of skin lesions and received many honours and awards.

12. Short Curriculum vitae

Peter Anton MIESCHER

Date of birth: 6 October 1923

Nationality: Swiss

Civil status: Married, two children

Family

Married in 1950 to Annatina Loetscher (1924), Dr. med., FMH Ophthalmology. She abandoned her own profession in order to assist PAM in his academic career, particularly in terms of teaching and organization. She obtained a New York MD degree and was appointed Instructor of Medicine at New York University. She ran the Clinical Pathology Course at NYU from 1960 to 1966. At Geneva University she was appointed "Chargé d'Enseignement" at the Medical Faculty. She ran the course on microscopic and chemical diagnosis for the medical students, and later the Practical Haematology Courses at Geneva University Hospital from 1969 to 1989.

Children:

Guido (1952), Dr. med., FMH Internal Medicine. Scientific Advisor, Swiss Science and Technology Council, State Secretariat for Education and Research, Berne. Married in 1981 to Sylvia Margaret Granger (1950), Ph.D. London University, Privat Docent at the Medical Faculty of the University of Berne, Chief of Immunology, CLB Behring AG, Berne.

Annatina (1955), Dr.med. Geneva University, M.D. New York, Clinical Assistant Professor of Psychiatry, Head of the Alcoholism Outpatient Program, Bellevue Hospital Center, Department of Psychiatry, New York University, New York

Education and further specialization

Universities of Lausanne and Zurich, 1942-1948 Dr.med. University of Basle, 1949 FMH Internal Medicine, Basle 1956

Academic degrees

Privat-Docent, Basle University 1957
Professor of Medicine, New York University, New York, 1959-1968
Professor emeritus, New York University, 1968
Professor at the Department of Medicine, in charge of Hematology, Geneva University, Geneva 1968-1994
Professor emeritus, Geneva University, 1994
Professor honoris causa, Beijing Medical University, People's Republic of China, 1986
Professor honoris causa, West China University of Medical Sciences, Chengdu, PRC, 1991

Consultantships, Awards, etc.

1959 Visiting professor, New York University, N.Y.

1963 Research Award of the City of Basle

1966 Visiting professor, Middlesex Hospital, London

1976 Belden Memorial Lecturer, Mayo Clinic, Rochester, Minnesota

1979,1980,1982 Blaffer Visiting Professor, MD Anderson Hospital and Tumor Institute, Houston, Texas

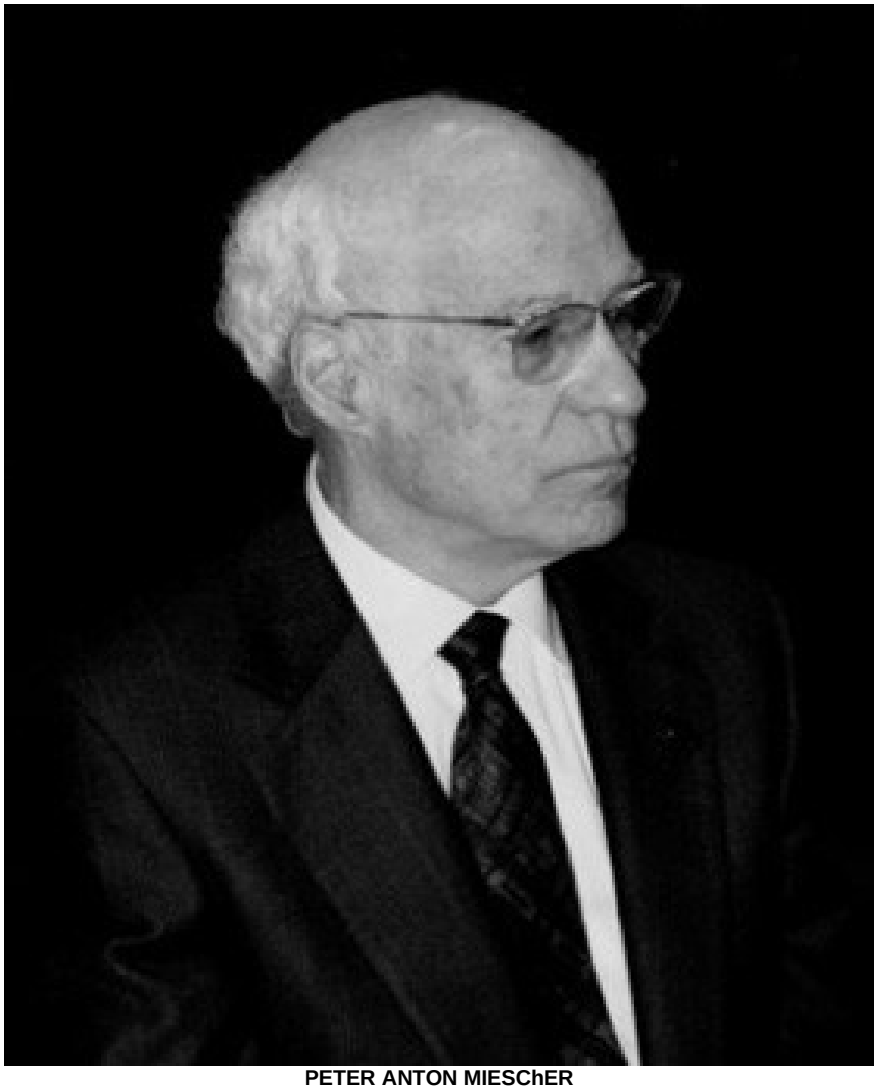
1983 Symposium on SLE on the occasion of PAM's 60th birthday, Geneva

1988 Consultant, Department of Orthopedics, Princess Grace Hospital, Monaco

1993 Founder of Centre for the Treatment of Autoimmune Diseases and Chief Consultant until 2000 at the State Hospital of the Republic of San Marino

2003 Honorary Advisor in Clinical Immunology at the S. Andrea Hospital, University La Sapienza, Rome

1981-2003 Honorary Advisor to several medical schools in Italy.



PETER ANTON MIESChER

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APPENDIX

List of 45 autoimmune diseases

- Alopecia Totalis
- Ankylosing Spondylarthritis
- Anticardiolipin Syndrome
- Aplastic Anemia
- Autoimmune Diabetes
- Autoimmune Myelodysplastic Syndrome
- Autoimmune Hemolytic Anemia
- Basedow's Disease
- Behçet's Syndrome
- Bullous Pemphigoid
- Chronic Active Hepatitis
- Churg Strauss Syndrome
- Cogan's Syndrome
- Crohn's Disease
- Cryoglobulinemia (mixed IgM-IgG)
- Dermatomyositis
- Discoid Lupus Erythematosus
- Hashimoto Thyroiditis
- Horton' Disease
- Idiopathic Chronic Thrombocytopenic Purpura
- Idiopathic Interstitial Pneumopathy
- Juvenile Idiopathic Arthritis
- Lambert Eaton Myosthenic Syndrome
- Lichen Planus
- Motor Neuron Disease with Splenomegaly
- Multiple Sclerosis
- Myasthenia Gravis
- Nephrotic Syndrome with Splenomegaly
- Pemphigus
- Pericarditis, Idiopathic with Splenomegaly
- Polyarteritis Nodosa
- Polymyalgia Rheumatica
- Polymyositis
- Primary Biliary Cirrhosis
- Psoriasis
- Rheumatoid Arthritis
- Sjogren's Disease
- Still's Disease
- Systemic Lupus Erythematousus
- Systemic Sclerosis
- Takaiasu Arteritis
- Ulcerative Colitis
- Uveitis, Idiopathic with Splenomegaly
- Weber Christian Disease
- Wegener's Granulomatosis

Diseases with Autoimmune Features

- Ig-A Nephropathy (Berger's Disease)
- Sarcoidosis
- Schoenlein Henoch's Syndrome

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