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GEORGE SARTON CHAIR

of the

HISTORY OF SCIENCES

1989-1990

G. SARTON MEMORIAL CHAIR LAUDATIO
for Prof. Sir E.P.Abraham, Oxford University, U.K.

THE PENICILLIN STORY : SAGA AND SCIENCE

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Prof. Sir E.P. Abraham, you belong to the great personalities, who played a major role in the penicillin saga. The full story of this monumental discovery is glorious, even fantastic and also fraught with human passion and-above-all scientific drive.

Names of the Nobel-laureates Alexander Fleming and of Howard Florey, Ernest Chain a.o., with whom you collaborated from the very early stages in the 1940's — and whose work and ideas you extended brilliantly at Oxford University up to now — sound familiar to layman.

No film scriptwriter could ever have invented such an exciting tale cast for larger-than-life actors and you are one of them.

At the centre of the stage was Alexander Fleming, working at St. Mary's hospital in London U.K., deputy to the legendary Almroth Wright, one of the fathers of vaccination who believed that the body can mobilise its own defences against disease. A. Fleming was one of the first to realise the value of lysozyme found in mucosa and saliva, as an antibacterial. This sparked off Fleming's interest in other antibacterials of natural origins. In the late 1920's he discovered *accidentally* that a *Penicillium* mould secreted a natural product which inhibited staphylococci. The isolation of the active ingredient, which he named penicillin, from the culture proved difficult. In vain he sought assistance from others including Raistrick and Clutterbuck, but by 1936 he gave up after having published all his findings.

In the late 1930's Florey, at the Sir William Dunn School of Pathology of Oxford University, gathered a team including Chain, Abraham, Heatley... to discover antibacterials for infective diseases. Very soon they renewed their attempts to extract, isolate and characterise penicillin. Step by step the Oxford group succeeded in this, until they reached the last hurdle, how to produce this antibiotic on a large scale.

Only surface culture had been used to produce penicillin but not enough could be made by this technique. In desperation, the U.K. government sent Florey to Northern Regional Research Laboratory of the U.S. Dept. of Agriculture in Peoria, Illinois, who had experience in growing *Aspergillus* moulds under submerged aerated fermentation. Peoria developed a medium based on cheap agricultural byproducts such as starch hydrolysate, lactose and corn steep liquor suitable for producing penicillin by submerged fermentation.

Eventually large scale manufacture of penicillin was made possible by the Americans and then spread worldwide. This development set standards for a worldwide search and interest in useful microorganisms and their products.

Those who still decry the profusion of antibiotics available to the medical or biological profession should reflect for one moment where we would have been if those pioneers — to whom you belong — had not persevered against all odds in unravelling these scientific and technical difficulties.

Thanks to you, most infectious diseases are today under control, although for some people : 'A medical drug is a shortcut to change disease'. Also, we all agree with the statement of the famous philosopher Schopenhauer :

'Health is not everything, but without health everything is nothing'. Indeed, the discovery and development of penicillin has not only served humans and improved their health directly or indirectly, it has also launched a frenetic search among microorganisms for other useful microbial products, which are now invaluable in human society to combat human, animal and plantdiseases. It has surely started interest in industrial microbiology, which is in fact the use of microbes to synthesize complex molecules (it is a subdiscipline of what is now called biotechnology).

Dr. E.C. Stakman has stated that 'microorganisms are among man's best friends (making antibiotics, vitamins, enzymes,...) but also his worst enemies (causing, disease, spoilage of food, materials, water,...) but that it took him a million years to find out'.

Prof. Abraham, your work and discoveries, including that on penicillin, cephalosporins, bacitracin,... have shortened this time-span considerably.

It goes beyond saying that the penicillin story is a historical milestone on the road of science development. In this respect, the life and work of Prof. Abraham fits completely within the scope and aims of the SARTON-committee. Indeed we are pleased that the present holder of the SARTON-chair is in the same way as George SARTON was — a person of richly faceted intellect and achievement, reaching from the lab bench to large biological industries.

You have set standards for those who followed : a long line of brilliant scientists and true humanist with interdisciplinary motivation and believing in symbiosis of sciences.

Sir Edward, you are convinced that knowledge, science ánd wisdom stand central to the individual's and to man's endeavours towards progress, although a bit of luck has often to be present (as illustrated by Dr. Fleming's '*accidental*' observation).

This is now often cited as a school-example of serendipity (which is, and I quote from the Oxford English Dictionary : 'The faculty of making happy and unexpected discoveries by accident', or easier to remember : 'Searching for a needle in a haystack, and finding a nice girl'.

Here, we should recall the words of Louis Pasteur — the first biotechnologist avant la lettre — : 'Chance only favours the prepared mind' (le hazard ne favorise que l'esprit preparé).

You were crucial in the development of fermentation industries, pharmaceutical and biotechnological companies all over the world, thereby applying *micro*biology to solve *macro*problems.

You played a key role in directing worldwide fundamental antibiotic research to meet practical challenges in biology, agriculture, medicine, fermentation, biochemistry and recombinant DNA research. Indeed your fundamental contributions — reflected in your numerous publications, books and lectures — on microbiology, biochemistry, enzymology, genetics and organic chemistry of now extremely useful or model microbial products — penicillin, bacitracin, cephalosporins, nisin, bacilysin... have set standards for other disciplines and products. Although several of these and similar compounds are made industrially in large quantities by fermentation, details about their biosynthesis, genetics remain to be solved and this is where fundamental research is essential. In this respect, a very famous scientist once said (I hope rather ironically) : 'Fundamental research is what I do when I do not know anymore what I am doing'; however he was a pure physicist rather than a biologist.

Sir Edward Abraham's eminent scientific career has been recognized and awarded with a series of worldwide honours, prices, patents, fellowships, medals,... and is now completed with the G. Sarton Memorial Chair (see c.v. below).

The endowment of a Knighthood in 1980 by the Queen of England deserves special mention.

Patents derived from the Oxford work on cephalosporins earned substantial royalties, since the worldsales of these antibiotics climbed in 25 years to more than 4 billion U.S. dollars per year. Charitable trust funds were set up with these royalties for support of medical, chemical, pharmaceutical and agrobiological research in several parts of the world.

Your wife Lady Asbjörg, which was a most charming host, when I stayed with my family in Oxford at the University and in your home, has been a fervent supporter and moral power behind the scenes of your scientific work and deserves our honours as well.

In overviewing the history and current state of industrial microbiology, we are struck by an underlying theme : mutually beneficial relations between what we use to call basic research and applied research. A century ago the largely practical investigations of L. Pasteur led to the establishment of microbiology, immunology and biochemistry as basic sciences. Much later the discovery and productions of antibiotics — in which you were very instrumental — by applied microbiologists provided tools crucial to the development of molecular biology. And now basic research in microbial genetics has returned the favour by supplying an array of new techniques useful to construct 'tailor made' microorganisms for industrial applications. This synergy between science and technology is the key to further progress in industrial microbiology, fermentation and biotechnology. Indeed, L. Pasteur's saying of exactly 100 years ago remains true : 'There are no applied sciences; there is only the application of sciences'. (il n'y a pas des sciences appliqués; il n'y a que des applications des sciences).

Prof. Sir E. P. Abraham's curriculum vitae is condensed here below :

ABRAHAM, Sir Edward (Penley), Kt1980; CBE 1973; FRS 1958; MA, DPhil (Oxon);
Fellow of Lincoln College, Oxford, 1948-80, Honorary fellow, since 1980; Professor of Chemical Pathology, Oxford, 1964-80, now Emeritus Professor; b 10 June 1913; s of Albert Penley Abraham and Mary Abraham (nee Hearn); m 1939, Asbjörg Harung, Bergen, Norway; one, s. Educ : King Edward VI School, Southampton; The Queen's College Oxford (1st cl. Hons sch. of Natural Science), Hon. Fellow 1973, Rockefeller Foundation Travelling Fellow at Universities of Stockholm (1939) and California (1948).
Ciba lecturer at Rutgers University, NJ, 1957; Guest lecturer, Univ. of Sydney, 1960; Reader in Chemical Pathology, Oxford, 1960-64. Lectures : Rennebohm, Univ. of Wisconsin, 1966-67; Squibb, Rutgers Univ., 72; Perlman, Univ. of Wisconsin, 1985; A.L.P. Garrod, RCP, 1986. Hon. Fellow : Linacre Coll., Oxford, 1976; Lady Margaret Hall, Oxford 1978; Wolfson Coll., Oxford, 1982; St. Peter's Coll., Oxford 1983. For. Hon. Mem., Amer. Acad. of Arts and Scis, 1983. Honn. DSc : Exeter, 1980; Oxon, 1984, Royal Medal, Royal Soc., 1973; Mullard Prize and Medal, Royal Soc., 1980; Scheele Medal, Swedisch Academy of Pharmaceut. Sciences, 1975; Chemical Soc Award in Medicinal Chemistry, 1975 Internat. Soc. Chemotherapy Award, 1983.
Publications : Biochemistry of Some Peptide and Steroid Antibiotics 1957; Biosynthesis and Enzymic of Penicillins and Cephalosporins, 1974, contribs to : Antibiotics, 1949; The Chemistry of Penicillin, 1949; General Pathology, 1957, 4th edn 1970; Cephalosporins and Penicillins, Chemistry and Biology, 1972; scientific papers on the biochemistry of natural products, incl. penicillins end cephalosporins.
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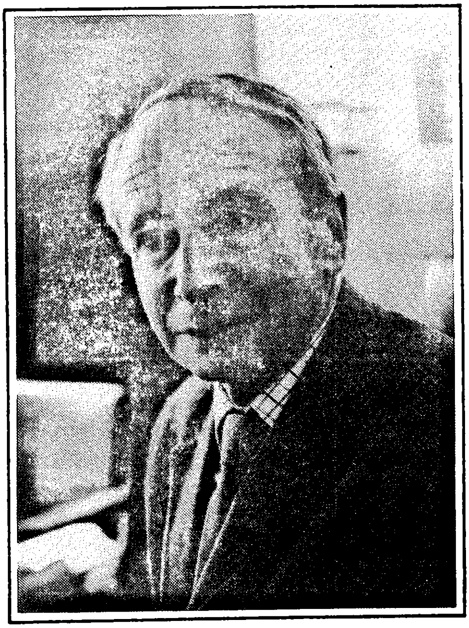

REFLECTIONS ON THE DEVELOPMENT OF THE PENICILLINS AND CEPHALOSPORINS

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Sir William Dunn School of Pathology,
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George Sarton was a pioneer of independent means who is widely acknowledged to be the founder of the history of science as an intellectual discipline. I feel greatly honoured to have been selected for the award of this Sarton Chair, particularly since I can make no claim to be a professional historian of science or medicine. But I have happened to live through the fifty years of what may be called 'the antibiotic era' and to have had the good fortune to be in personal contact with some of the ways in which it has developed and the people who figured in it.

In a previous and intriguing Sarton lecture Robert Merton, a student and friend of Sarton, spoke on 'The Matthew effect in Science'. He was concerned with the distribution of credit and reward in science and went for his title to the first gospel where a parable is used to explain how it can be that to those who have shall be given, but from those who have not even that which they have shall be taken away. The present lecture will be in some respects somewhat more specific. But I will try to indicate how chance events, scientific curiosity, personalities, industry and government policies were all involved in developments that led to one of the great medical advances of the 20th century. Little more than fifty years have passed since the time when physicians could do little in the face of life-threatening bacterial infections, when bacterial endocarditis was almost invariably fatal and meningococcal meningitis left its few survivors with pitiable disabilities.

Observations of the activity of some microorganisms against others and the idea that microbial products might have therapeutic use can be traced back at least to the time of Lister and Pasteur, but the early observations had little impact on medicine. There are several reasons why this was so. Time has shown that only a very small proportion of such substances have a low enough toxicity to man to be injected safely into the blood stream; many of the earlier observations were made by microbiologists who had no chemical or biochemical collaborators; and the methods available for the isolation and characterisation of substances from natural sources were far less advanced than they are today.

In World War I Alexander Fleming studied the effect of a number of antiseptics applied locally to war wounds and came to the conclusion that those in common use were not only ineffectual but harmful, because of their toxicity to animal cells. By the end of the nineteen-twenties it was widely believed that searches for a substance that was highly active against pathogenic bacteria but innocuous to man would be fruitless. That this pessimism was not justified became evident only a few years later after the chance discovery of an antibacterial substance that was not a product of the microbial world but of the dye industry. Following the interest of Paul Ehrlich in the selective staining of dyes, Domagk tested a number of dyes synthesised by the I. G. Farben industry. He found that one of them, prontosil, would protect mice from streptococcal infections. It is fortunate indeed that his tests were done *in vivo* and not in the test tube, for prontosil is inactive *in vitro*. Soon after Domagk's finding prontosil was shown by others to be split in the body to an inactive compound and to sulphanilamide, the first of the sulphonamides.
Sulphanilamide had been described in the chemical literature in 1908, but there had been no reason to suspect that it would have chemotherapeutic properties and it had never been tested for antibacterial activity.

The sulphonamides caused a dramatic reduction in deaths from streptococcal infections, particularly those responsible for puerperal fever in childbirth. Incidentally, a sulphonamide provided my first encounter with a clinically useful antibacterial substance. Just after the outbreak of World War II, when I was Rockefeller Fellow in Stockholm, I became infected with a streptococcus. My Swedish physician told me that unless I took the tablets he had prescribed I should only be travelling home, if at all, in a wooden box. So I took the tablets, managed to reach Oxford alive, and became involved in research on penicillin. However, the sulphonamides had serious limitations; they were not very effective, for example, against infections with staphylococci.

Fleming's good fortune

Domagk should have counted himself fortunate that prontosil was included among the azo dyes that he tested, for he did not realise that it was a colourless derivative of this dye which was medically important. The role of chance was far more striking, however, in Alexander Fleming's discovery of penicillin in 1929. Despite his discouraging experience with antiseptics in the local treatment of war wounds, he was not looking for a better substance. He had been asked to write a review on the staphylococcus and left plates of nutrient broth seeded with this organism on his laboratory bench while he went on vacation. On his return he noticed that one of these plates had been contaminated with a *Penicillium* and that in the area around this fungus the staphylococci appeared to be undergoing lysis. But, since penicillin lyses growing staphylococci but not those in fully grown cultures, how did this phenomenon occur ? Ronald Hare, a contemporary of Fleming, established that a spell of cool weather happened to be followed by a warm spell at that time. The *Penicillium*, grows best at a lower temperature than the staphylococcus. Hence the fungus could have grown and secreted penicillin before the staphylococcal colonies were fully established.

It is to Fleming's great credit that he did not ignore his unexpected discovery, although it was extraneous to the work he had in hand. He preserved the fungus and grew it to obtain an active culture fluid and gave the name penicillin to this 'mold broth filtrate'. He showed that this solution was highly active against some bacteria, but not others, and that it was not toxic to white blood cells and to a rabbit.

Fleming made some use of his 'mold broth filtrate' as a dressing for septic wounds, but said later that there was no miraculous success.

He then appeared to lose interest in penicillin as a therapeutic agent event after the advent of the sulphonamides and in 1940 wrote that 'the trouble of making it seemed not worth while'. It is of interest to speculate why this was so and why he never tried to find out, as he might have done, whether it was able to protect mice from lethal streptococcal and staphylococcal infections when injected into the blood stream. The answers to these questions probably lie in his personality, which was not conducive to his entry into a new field; in the discouraging climate of opinion at the time; and in the fact that he was not equipped, as a medical bacteriologist, to grapple with the problem of handling and purifying a relatively unstable substance.

However, Fleming's good fortune extended beyond the unusual events that enabled him to bring penicillin to light : he lived to obtain the lion's share of the public acclaim after others had revealed the outstanding importance of this discovery. Whether this provides an illustration of the Matthew effect I hesitate to say. But it clearly demonstrates the power of the media to influence the public's perception of history.

Florey, Chain their colleagues and the rôle of chance

The dramatic transformation of penicillin from little more than a curiosity to a substance of great therapeutic value came, more than ten years after it had been revealed by Fleming, with the discovery in Oxford of its ability to cure systemic bacterial infections — first in mice and then in man. How did this come about ? The stage for the new development was set by Howard Florey, an Australian who came to Oxford as a young man to study physiology and became a University Professor of Pathology in the Sir William Dunn School of Pathology in 1935.

Florey had first wished to study chemistry, but was advised that there were few jobs for chemists in Australia at that time and he therefore turned to medicine. But he retained a strong interest in chemical substances with biological activity, one of which was the bacteriolytic enzyme lysozyme that had been discovered by Fleming in 1921. He was convinced that this subject needed the collaboration of experimental pathologists with those in other disciplines and when he obtained the Chair in Oxford he found positions for chemists and biochemists in his Department. The first to come was Ernst Chain, a refugee from Hitler's Germany. He was followed by Norman Heatley and then, in January 1940, by me.

At Florey's suggestion Chain began to study the mode of action of lysozyme and during this work made a survey of the extensive literature on antimicrobial substances produced by microorganisms. In the course of many discussions in 1937-1938 with Florey, who drew his attention to a review of the field by Papacostas and Gaté in 1928, Chain suggested and Florey agreed that a systematic investigation of such substances should be undertaken. Three substances were first chosen for study and one of them was penicillin.

Chance intervened in several of these events and those that followed. Florey's election to the Chair of Pathology in Oxford nearly failed to occur, because his strongest supporter was late for a crucial meeting of the Electoral Board and only arrived just in time to prevent the despatch of an offer to another candidate. Florey's first choice for a chemical collaborator turned out to be unavailable and Chain was suggested in his place by Gowland Hopkins at Cambridge. Heatley had planned to go to Denmark in the autumn of 1939 to work with Linderstrom-Lang, but was prevented form doing so by the outbreak of war. And had it not been for the war and the reorganisation of research to which it led it is unlikely that I would have become a member of the Sir William Dunn School of Pathology when I returned to Oxford from Sweden.

However, the war, or the prospect of war, was in no way responsible for the decision to investigate naturally occuring antimicrobial substances. What motivated this decision ? One factor was probably the poverty of the School of Pathology in the 1930's and the knowledge that a grant from which Chain was paid was coming to an end; a project that might attract a new grant was thus highly desirable. Another was that the project appeared to be one of wide scientific interest. Both Florey and Chain insisted later that they had no expectations that it would yield results of clinical value. Indeed, Chain wrote that he had believed penicillin to be a microbial protein that would provoke an immune reaction and thus be disqualified from systemic medical use. Florey stated in a short recording of his life : "I don't think that the idea of helping suffering humanity ever entered our minds". Nevertheless, in subsequent applications for support from the Rockefeller Foundation and the medical Research Council it was mentioned that the study might lead to medically useful substances. Perhaps this is an example of a not uncommon tendency of academic applicants for grants to point to the possible utility of the research they propose in the hope that this will increase the chance that their application will be successful.

But why was penicillin included in the substances chosen for study ? Chain stated that he regarded the reported instability of penicillin as a challenge to the biochemist and Florey appears to have been interested in its activity against the staphylococcus. In any event, it was by great good fortune that the choice was made, for in 1949 Florey could say that the outcome was so gratifying as to be almost unbelievable.

I do not propose here to go into the details of the work which led to Florey's demonstration in May 1940 that penicillin would cure generalised infections in mice and then to the first clinical trial in the

Radcliffe Infirmary in Oxford. But it may be of interest to recall some of the problems that arose and the attempts to overcome them.

One major problem, of course, arose from the minute amount of penicillin (about 1µg/ml) that was produced in surface culture by Fleming's *Penicillium notatum*. Moreover, some of the fermentations failed because of contamination with bacteria that produced a penicillin-destroying penicillinase, a type of enzyme that we discovered in 1940 in *E. coli*, while looking for an explanation of the fact that some bacteria were relatively resistant to penicillin.

Heatley achieved a ten-fold purification of the early penicillin-containing extracts by transfer between solvents. Nevertheless the resulting purity of product used in the mouse experiments was probably less than 0.1 and 0.2%. The purity of most of the material prepared subsequently for clinical trial was between 2 and 3%. It was fortunate indeed that the great mass of impurity in these early preparations was itself relatively innocuous, for if it had been toxic the therapeutic power of penicillin would have been concealed. However, the first penicillin to be injected into a patient produced a disconcerting rise in temperature and a rigor and a second patient reacted similarly. But fortunately it was soon shown that this was not caused by penicillin itself for by that time I had introduced a chromatographic step into the purification process which removed the pyrogenic material.

Larger scale production

The success of the early clinical trials and the potential value of penicillin for the treatment of war wounds made it evident that serious attempts should be made to produce enough penicillin for it to become widely available. Florey decided that this would not be possible in war-time Britain, then under heavy bombing, and he went with Heatley to the United States, where he had good friends, to enlist American support. This visit produced gratifying results, although it did not enable Florey to obtain the penicillin he urgently needed for further clinical trials. At the Northern Regional Research Laboratory in

Peoria, where Heatley described the current Oxford process, fermentation in deep aerated cultures was introduced and production stimulated by the addition of corn steep liquor, a by-product of the maize industry that was readily available in the Mid-West. Later, after a world-wide search for higher yielding strains of *Penicillium*, a superior strain of *Penicillium chrysogenum* was isolated by the group at Peoria from a mouldy canteloupe in the local market. Eventually the yield of penicillin obtained by fermentation in pharmaceutical companies was more than ten thousand times that produced originally by surface culture in Oxford. George Merck later explained to me why very little American penicillin came to Oxford : it was commandeered, he said, by the armed forces.

Despite this disappointment enough penicillin was obtained in the Sir William Dunn School of Pathology and from commercial British sources for a further clinical trial by Howard and Ethel Florey in 1942. The patients with very serious infections included one with a sulphonamide-resistant streptococcal meningitis and ten with either staphylococcal-osteomyelitis, septicaemia or cavernous sinus thrombosis. All these patients recovered after penicillin had been administered by intramuscular injection and there were no toxic effects. In addition, mastoid infections were treated locally and successfully by instilling penicillin, after mastoidectomy, through a tube sutured into the wound. This type of procedure involving early suture and the instillation of penicillin was used with success in North Africa when Florey and later Hugh Cairns went there in 1943 to study the best use of the still trivial amounts of penicillin available for the treatment of infected war wounds.

Isolation, structure and attempted synthesis of penicillin

When Florey had visited American pharmaceutical firms in 1941 some, including Merck, Squibb and Pfizer were seriously interested in penicillin production, others less so and some not at all. One reason for a lack of wider enthusiasm was probably the formidable difficulties that would face commercial production with the trivial yields of penicillin obtainable by fermentation at that time. But another may well have been the expectation that fermentation would be supplanted by total chemical synthesis. Fleming had been bold enough to prophesy in 1940 that penicillin would not be used in war surgery "until some chemist comes along and finds out what it is and if possible manufactures it".

Before rational attempts could be made to synthesise penicillin it was clearly necessary to know its structure. Clutterbuck, Lovell and Raistrick had abandoned an attempt to isolate it in 1932. Chain and I began to purify penicillin in 1940 and by 1942 we had a product which proved later to be nearly 50% pure. Chain was so excited by the high antibacterial activity of this product that he became optimistic enough to say to me that nothing could be so active if it were not pure. But almost a year elapsed before we obtained nearly pure material. By this time we had isolated several characteristic degradation products of penicillin and had begun to collaborate with Professor Sir Robert Robinson and Dr Wilson Baker in the Dyson Perrins organic chemistry laboratory in Oxford, while work in a number of American Institutions was under way. In July 1943 our earlier belief that sulphur was absent from the penicillin molecule, based on the failure of a micro-analyst to find it, was shown to be wrong.

In august 1943 a telegram from Squibb gave the exciting news that their penicillin had been crytallised as a sodium salt. I then converted our purest material, which was in the form of a barium salt, to a sodium salt and the latter was found to crystallise spontaneously. It was evident, however, that the British and American penicillins were not identical. They had a common nucleus but different side-chains, due to the presence of a side-chain precursor in the corn steep liquor added to the American fermentations.

By October 1943 it seemed clear that the penicillin structure was to be obtained by the removal of the elements of water from a known degradation product of penicillin. But how was this to be done ? On the basis of my finding that penicillin contained no basic group, I proposed the well known ß-lactam structure in October 1943.

However, Sir Robert Robinson disliked this structure intensely and proposed an alternative one. Controversy continued until 1945, when a crystallographic analysis by Dorothy Hodgkin and Barbara Low finally showed that the ß-lactam structure was correct.

Immense efforts were made in Britian and the United States during the war to synthesise penicillin — many of them with the wrong structure in mind. But despite the activities of at least a thousand chemists in some thirty-nine major laboratories, only traces of the drug were ever obtained. One reason was the unavailability at that time of a reagent that was mild enough to close the four-membered ß-lactam ring without inactivating the resulting penicillin. A few years after the war such a reagent was found by John Sheehan at MIT, who used it in a rational synthesis of penicillin. However, the production of penicillin by fermentation had then become so efficient that chemical synthesis had no chance of competing with it. Later, however, chemical studies were to make major contributions to the field.

The penicillin nucleus and new penicillins

At the end of the war the astonishing therapeutic properties and the limitations of penicillin were well established. It seemed possible that the final chapter in the history of its great contribution to bacterial chemotherapy had already been written and indeed that its value might decline because of the emergence of resistant bacteria. A number of penicillins with different side-chains were obtained in the Eli Lilly laboratories by the addition of appropriate precursors to the fermentation, but the type of side-chain that could be introduced in this way was limited and the resulting compounds were not clearly superior in antibacterial activity to the original penicillins.

However, two unpredictable events changed this situation. One was the isolation of the nucleus of the penicillin molecule, 6-aminopenicillanic acid, and the other was the discovery of the first cephalosporin and the production of its corresponding nucleus, 7-aminocephalosporanic acid. To these nuclei innumerable side-chains could be added by chemical procedures.

The penicillin nucleus was first observed by Sakaguchi and Murao in Japan in 1950. They reported that it was formed when the side-chain of benzylpenicillin was removed by an enzyme in *P. chrysogenum*. Three years later indirect evidence for its existence in fermentations to which no side-chain was added was obtained by Kato, also in Japan. But these findings were not pursued further in Japan and we may ask why this was so, since an important development was in sight. One reason was that the Japanese workers had no chemical collaborators, and another was that Murao and Kato went to other institutions where there was little interest in penicillin research. However, in 1956 Batchelor and Robinson independently made observations similar to those of Kato while working in Chain's laboratory in Rome. After their return to Beecham they concluded that their results were due to the presence of the penicillin nucleus (6-APA). In 1958 this substance was isolated and characterised and a series of new and clinically valuable penicillins with an extended range of activity was then obtained from it by semi-synthesis.

Chance and the Cephalosporins

The discovery of the cephalosporins came from a decision of Giuseppi Brotzu, a Sardinian medical bacteriologist who had been Rector of the University of Cagliari and was later Mayor of the city, to look for new antibiotic-producing organisms near a sewage outfall. He supposed that the self-purification of sewage was partly due to antibiosis. Although it is doubtful whether this idea was well-founded, he quickly isolated in 1945 a *Cephalosporium* fungus that produced material with a broad range of antibacterial activity. He boldly injected this crude material into patients and concluded that it had a beneficial effect, particularly in cases of typhoid fever. But he had neither the facilities nor the expertise to carry these observations further and his attempt to arouse the interest of an Italian pharmaceutical company was unsuccessful.

Brotzu then wrote to a British acquaintance who consulted the Medical Research Council in London and it thus came about that he kindly sent his organism and a copy of a publication, entitled 'Richerche' su di un Nuovo Antibiotico', to the Sir William Dunn School of Pathology, Oxford, in 1948. For some time we imagined that this paper was a contribution to an unfamiliar Sardinian journal called 'Lavore dell'Istituto d'Igiene di Cagliari'. But years later, when I met Brotzu for the first time and asked him how often this journal appeared, he smiled and said that it had never appeared before or since but that there would be a second issue if he made another discovery that was of comparable interest. Had it not been for an unforeseen sequence of events it is highly unlikely that we would have been aware of his work.

It turned out that what Brotzu had described as 'A new antibiotic' was in fact a mixture of at least seven different antibiotics. Five of them were acidic steroids extractable by organic solvents.

However, it became clear to me that this group of substances could not have alone been responsible for the broad range of activity observed in Sardinia. I therefore studied the aqueous solution remaining after their extraction and found that it contained a different antibiotic with a wider range of activity. In deciding to investigate this substance further, my colleague Guy Newton and I were not at first motivated by the expectation that it would be of value in medicine, but by the fact that it had some of the chemical and physical properties of an unstable peptide and might therefore belong to a class of substances in which I had been interested since my earliest days of research. In the event we showed that it was a peptide-like penicillin with a new type of side-chain, consisting of an amino acid, which endowed it with a new type of antibacterial activity. It was finally named penicillin N.

Penicillin N was undoubtedly the antibiotic whose activity had been detected by Brotzu. It received a small clinical trial in Mexico and was reported to be superior for the treatment of typhoid to the widely used and quite different antibiotic chloramphenicol. But it was never produced commercially. One reason for this may have been that it was difficult to purify and that its large-scale production would not have been financially rewarding.

However, it was the difficulty of purifying penicillin N and our interest in its structure that led Newton and me to the discovery in 1953 of a third antibiotic which was the first of the group of compounds now generally known as the cephalosporins. This substance, which we named cephalosporin C, was present as a minor impurity in our preparations of penicillin N. But it was readily separated from the product obtained when penicillin N was inactivated by dilute acid and it then crystallised as a sodium salt, and it was only shown after its isolation to have antibacterial activity.

We had two incentives to pursue a study of cephalosporin C. One came from the finding that it resembled penicillin N in having an amino acid-chain attached to a four-membered ß-lactam ring. These resemblances to a penicillin led us to hope that it would be relatively non-toxic. Another was the finding that cephalosporin C was resistant to hydrolysis by a penicillinase that hydrolysed the original penicillins then known. At that time the emergence of staphylococci in hospitals that were penicillin-resistant because they produced a penicillinase was becoming a serious medical problem and it seemed that penicillin might lose one of its most important properties.

What was the nature of the structural difference between the penicillin and cephalosporin molecule ? In our attempts to establish this by the methods of classical organic chemistry, Newton and I encountered more difficulties than we had anticipated, despite the fact that we received help in the production of material by a small Antibiotics Research Station that had been set up by the Medical Research Council.

However, while thinking about our problems during a skiing holiday in the spring of 1958, I decided that the only possible structure was one in which a ß-lactam ring was fused with an unsaturated six-membered ring instead of with the saturated five-membered ring in penicillin.

It was not immediately obvious that this structure would account for the absorption of cephalosporin C by ultraviolet light and at first not everyone was willing to accept it. In 1960, on the evening before I was due to present our compelling evidence for it at a meeting in Australia, I was disconcerted to receive a telegram from London which stated baldly 'your structure believed to be wrong'. I could only try to ignore this telegram. But on returning to Oxford through America I stopped at Harvard and showed the structure to R. B. Woodward, perhaps the post eminent organic chemist of his generation. He remarked 'If I had proposed that structure for a compound with that absorption spectrum I would be very unhappy'.

Despite these events there was no prolonged controversy over the structure for cephalosporin C, as there had been over that for penicillin, for Dorothy Hodgkin, to whom we have given crystals of cephalosporin C soon after they had first been obtained, completed an X-ray crystallographic analysis with E.N. Maslen which comfirmed the structure that had been proposed.

Arguing by analogy with penicillin N and other penicillins we were tempted to make a number of predictions about the biological properties of this structure, some of which turned out to be true while others did not. We expected that appropriate changes in the amino acid side-chain of cephalosporin C would result in a large increase in activity against certain bacteria. We showed that this was so and also that interesting changes in activity followed changes that could be made in a group attached to the six-membered ring. On the other hand our naive hope that the resistance of cephalosporin C to staphylococcal penicillinase would extend to penicillinases from almost all other bacteria was highly optimistic, for time has revealed the existence of a multiplicity of such enzymes with different substrate profiles. We also hoped that many cephalosporins would be well absorbed when given by mouth, because they were relatively stable to acid and would thus be able, like penicillin V, to survive gastric acidity. But in fact it was several years before the first orally active cephalosporin was produced. Finally we thought that the structural difference between the penicillin and the cephalosporin nucleus might enable penicillin-sensitive individuals to be given cephalosporins with impunity. Although this has appeared to be true in many cases it is not so in all. It is evident that these biological phenomena are too complex at the molecular level for predictions based on simple analogies to have a high chance of success.

Development by pharmaceutical companies

Florey showed that cephalosporin C itself would protect mice from lethal infections with penicillin-resistant staphylococci and that it was even less toxic than penicillin G. He believed that it would find a use in medicine and it was in fact used succesfully in a few cases, but there were two reasons why it did not come into general use. First, the isolation of the penicillin nucleus was followed by the semi synthesis of new penicillins, one of the first of which, methicillin, could cope with penicillin-resistant staphylococci. Secondly, semi-synthetic cephalosporins that were much more active than cephalosporin C could be obtained from the nucleus of cephalosporin C.

Two pharmaceutical companies, Glaxo and Eli Lilly, showed serious interest in cephalosporin at an early stage. Glaxo's involvement was stimulated by Florey's acquaintance with its then Chairman, Sir Harry Jephcott. Eli Lilly were particularly interested because they had been hoping to isolate the penicillin nucleus but had been forestalled by Beecham.

An unforeseen difficulty faced the large-scale development of the cephalosporins. The penicillin nucleus could already be obtained by removal of the side-chain of penicillin G with an enzyme, but no enzyme that would remove the side-chain of cephalosporin C should be found.

We had obtained the nucleus of cephalosporin C by mild acid treatment, but only in very low yield. However, in the Lilly Research Laboratories a chemical process was devised for preparing this nucleus in quantity. This opened the way to the study of innumerable cephalosporins with different side-chains.

Among the many thousands of semi-synthetic cephalosporins produced by pharmaceutical companies and containing a variety of different side-chains and substituents on their six-membered ring, twenty or more have proved to be of value in medicine. They have extended the range of bacterial chemotherapy from the staphylococcus to a number of Gram negative bacteria, including some that are penicillinresistant, and share with the penicillins the indispensible property of low toxicity. In short, they can be regarded as complementary to the penicillins and have an important place in the search for new non-toxic substances that can cope with the continuing emergence of new resistant organisms. The considerable demand for these substances by clinicans, has led to world sales that are now said to be nearly £4,000 million per year.

Oxford and patents

This brings me to another unanticipated aspect of our involvement with the cephalosporins. Before and during the war it was widely felt that commercially valuable findings by those in academic medical research should be made freely available. This view was held in Britain by the then President of the Royal Society and the Secretary of the Medical Research Council and in the USA by members of the Rockefeller Foundation. Chain, whose father had been an industrial chemist, made strenuous efforts to change these views with respect to penicillin, but was entirely unsuccessful. In retrospect I doubt whether a rewarding patent for the Oxford work on penicillin could have been obtained, at least after the publication of the clinical paper, but it was a principle that was at stake.

Towards the end of the war, however, when thoughts were turning to post-war reconstruction, it appeared to the British Government that a failure to exploit and protect scientific discoveries had imposed a significant financial loss on the country. An outcome of this conclusion was the setting up of a National Research Development Corporation (NRDC) to support potentially valuable inventions in the national interest and a volte-face by the Medical Research Council.

At an early stage of our work on the products of Brotzu's *Cephalosporium* I was surprised to receive a letter from the Medical Research Council expressing the hope that we would patent, through NRDC, findings that might be of medical value.

At that time (though no longer) the University of Oxford disclaimed any interest in patent royalties and its members were free agents provided only that they did not use the University's name in commercial transactions. In fact we assigned cephalosporin patents to NRDC, which carried out all negotiations with pharmaceutical companies but had a standard revenue sharing agreement with inventors. Our key patents were cephalosporin C and its nucleus.

When royalty payments from NRDC began to come in, at first in relatively small amounts, I began to think about what to do with the money. I soon decided, with my wife's encouragement, to divert most of my royalties into two Charitable Trust Funds, the first to support medical, biological and chemical research in the University of Oxford; and the second to include education as well as research in these sciences and the Royal Society and an independent school among possible beneficiaries. Guy Newton, who had less to dispose of because he had been employed by the Medical Research Council as well as by the University, told me that he wished to set up a smaller Fund.

The setting up of charitable Trust Funds was not a simple legal procedure, for my lawyers told me that it might be claimed that I had disposed of a marketable asset and was thus liable for a substantial tax on what had been given away. Fortunately, however, the Board of

Inland Revenue eventually agreed that such tax would not be claimed. Had they decided otherwise I do not know what we should have done. One adviser suggested that we should emigrate, but this was a painful solution that we never seriously contemplated.

The income from these Trust Funds has so far enabled the Trustees to endow three Chairs and a variety of Fellowships and to support many new developments in the medical, biological and chemical sciences.

Comments on the past and prospects for the future

Sir William Dunn left the residue of his estate for the relief of human suffering. The money was partly used to build the Sir William Dunn School of Pathology in 1927, but only after a High Court ruling that this would not conflict with the benefactor's intentions. It now seems clear that the Dunn School has been able to comply with the terms of Dunn's Will.

Unlike most of the later antibiotics of clinical value the first penicillin and cephalosporin came from academic institutions in which research was largely motivated by scientific curiosity. But a good many years elapsed between the early discoveries and the wide use of these families of antibiotics in medicine that was only made possible by the skill and resources of the pharmaceutical industry.

For pharmaceutical companies the finding of products of commercial value is a prime objective of research and comes before a disinterested pursuit of scientific knowledge. The academic's need to publish and a company's wish to protect its property are possible sources of friction in a collaborative enterprise. But I can say here that we encountered no serious problems of this kind in our relationship with NRDC and its licensees. Moreover, in assessing what was done in pharmaceutical companies it would often be difficult to distinguish between applied and basic research.

In the present lecture I have emphasised the roles of chance and luck. But good luck often needs to be complemented by the gift of some ability. During a discourse in 1854 Pasteur told his audience to remember that in the field of observation "Le hasard ne favorise que les esprits préparés"; and later Paul Ehrlich included patience, skill and money, as well as luck, in his list of four helpful things in scientific research — Geduld, Geschick, Gluck, Geld.

Despite the remarkable contributions to medicine that have been made by the penicillins and cephalosporins now available, strains of bacteria with resistance to them continue to emerge, particularly in hospitals. Thus the search for new compounds has not come to an end. More sensitive methods have been introduced for screening the microbial world. Rapid progress is being made in the isolation of genes that code for enzymes involved in the biosynthesis of ß-lactam antibiotics and in resistance to them. With such fundamental knowledge a less empirical approach to this area of chemotherapy may eventually be feasible.

Sarton Medal Lectures

LAUDATIO A. EVRARD

Michel Thiery, Gent

The board elected Professor Alexander Evrard as recipient of a 1989-90 George Sarton Commemorative Medal because of his personal contribution to the study of the history of neuro-psychiatry and his active participation in the academic teaching of the history of medicine, by which Evrard helped to resurrect a longstanding tradition of the University of Gent, where a compulsory course of the history of medicine was first introduced in 1835. Later, the subject matter became optional and the course was finally dropped altogether around the turn of the century. Many teachers nevertheless attempted to fill up what they considered to be a gap by starting their course with a historical overview of the subject. This tradition too vanished gradually, to the extent that after World War II, only the Professor of Bacteriology used to treat his students to an opening lecture on the epic work of his famous predecessors, the "microbe hunters".

Interest in the teaching of medical history revived in the early 1950s when an Emeritus Professor of the Free University of Brussels, wishing to perpetuate the memory of his son — the late Egyptologist Frans Jonckheere, MD — funded the establishment of a lecture course on this subject in our university. The medical Faculty became the recipient of the Jonckheere Memorial Lectures, which were initiated in 1957 by the head of the Department of Physiology, Professor Jean Van de Velde. After Van de Velde's untimely death, this task was taken over by the famous medical historiographer Professor Léon Elaut who in 1966 was succeeded by the then *chef de clinique* of the Department of Neuro-psychiatry Dr. A. Evrard. Snowed under by other commitments, Evrard resigned from the course in 1970. Because no candidate could be found to succeed him, the course was interrupted until the academic year 1977-78, when Dr. Pharm. Leo Vandewiele — Ph. D. in the history of pharmacy and future laureate of the George Sarton

Memorial Chair (cfr. *Sartoniana* 2 : 11, 1989) — volunteered to resume the lectures. Having himself reached the age of retirement in 1979, Vandewiele proposed a licentiate in history as his successor. Regretfully, however, the Medical Faculty declined this gracious offer on the grounds that medical students should be taught the historical background of their profession-t-be by someone belonging to it. Thus, for the second time, the teaching was interrupted. It was finally rescued thanks to the initiative of the then Dean, Professor A. De Schaepdryver, who since 1981 has each year invited a number of local and foreign speakers to read papers on a wide variety of topics related to the history of medicine. This new formula has proven attractive to students and graduates of other faculties as well. Due to the efforts of the Chief Editor, Professor I. Leusen, the texts of these lectures have been printed in the *Tijdschrift voor Geneeskunde*, the principal medical journal of Belgium. This has of course promoted the popularity of the project.

Ladies and Gentlemen. My short introduction has given you a glimpse of Professor Evrard's many interests ad activities. Let me proceed now in a more regular fashion. Factually, this will not be difficult for me, because Alex and I have known each other for ages : we did our premedicals together and later our academic careers ran virtually parallel. No, what makes me a little uneasy is that Alex hates eulogy. In point of fact he is a very modest man, utterly reserved and almost shy. To give you one example of his idiosyncrasy about praise : when Evrard was granted the freedom of the State of Texas in 1964 for his personal efforts in the areas of cultural exchange and care of handicapped children, non of his friends and colleagues was informed by Alex about this exceptional honour which had been bestowed on him. When approached recently by a member of the Sarton committee, our "freeman" was startled because, in his mind, there was a gross discrepancy between the hónor we wished to pay him and his personal contribution to the history of medicine. For all of these reasons, my representation must be brief and to the point.

Alexander Karel Evrard was born in Ledeberg, a suburb of Gent, on December 15th in 1923. Having completed his classical humanities at the Jesuit college he studied medicine at the University of Gent, where he obtained the MD diploma in 1950. After a short stay at the Psychiatric Clinic of the University of Leiden (The Netherlands), Alex returned to his Alma Mater as an assistant to Professor J. De Busscher. Five years later, he was qualified in neuro-psychiatry. Alex made the most of his several stays at Dutch clinics, in particular the department of the famous Professor Carp and the section of child psychiatry directed by Dr. Van Krevelen. In 1953, he defended at the University of Leiden his thesis on the *Patho-psychologic significance of the negativistic attitude* which earned him his second MD diploma. Doctor Evrard then returned to the University of Gent, which he has not left since. Here, he was appointed successively *chef de clinique* of the Department of neuro-psychiatry, deputy of Professor Vander Eecken for clinical demonstrations in child psychology, and lector of psychiatry. Finally, in 1969, he became Associate Professor in the Medical Faculty and shortly after that, full professor.

I shall spare you the list of the subjects taught by our laureate of today. Those interested can read it in the Yearbook of the University of Gent, where it covers an entire page. Suffice to say that the staple of his theoretical lessons is concerned with general and applied psychology and the care of the handicapped. In his out-patient clinic the professor supervises two sections : one for medical psychology, belonging to the Faculty of Medicine, the other a training school for handicapped connected with the Faculty of Psychology and Education.

Evrard has always been fascinated by the historical background of his profession which, at the age of 32 inspired him to write his first book *History of Psychiatry*, which was followed by many papers and countless lectures dealing with a variety of medical-historical subjects related to psychiatry.

But it would wrong our laureate if I did not allude to his printed scientific medical work which is considerable : five books and fourscore articles in national and international journals. As already mentioned, Evrard is also a fêted speaker as he will justifiably prove to his audience today.

Ladies and Gentleman. This must be the end, because I perceive that our colleague is becoming a bit nervous, which for a professional psychiatrist is an ominous sign.

Dear Alex. Do be convinced that the honor bestowed on you today is entirely deserved. And do accept our tribute as a token of thanks for your contribution to medical historiography and your effort to keep alive the teaching of medical history at our university.

UN SIECLE DE PSYCHIATRIE

A. Evrard

En esquissant l'évolution psychiatrique, on constate qu'il s'agit d'une science que l'on pourrait nommer encore jeune.

Pour nos contrées, les premiers essais systématiques datent de Joseph Guislain (Gand, 1797-1860), qui fut notre premier aliéniste (le terme "psychiatrie" ne fut introduit qu'en ce même 19e siècle par Reil à Halle, Allemagne).

Grand médecin et grand savant, Guislain est néanmoins entré dans l'histoire surtout comme un précurseur et un pionnier social : tout comme Pinel en France, comme Tuke en Angleterre, et comme Schroeder van der Kolk en Hollande, il fut l'humaniste et le philanthrope qui s'efforça à changer le misérable sort des "fous", un des promoteurs européens de la transformation des cachots en hôpitaux psychiatriques.

La plupart des auteurs ne situent vraiment le début de la psychiatrie scientifique que vers la transition de siècle, notamment avec Emil Kraepelin (Münich) qui introduisa les termes de psychose maniaco-dépressive et de démence précoce (qui fut par-après ré-baptisée en schizophrénie par le Suisse Eugen Bleuler).

Il semble assez évident qu'en cet aperçu il ne peut être question d'établir toute l'histoire de cette branche de la médecine qui s'occupe des maladies mentales, même s'il ne s'agit que d'une évolution pendant environ un seul siècle.

Nous nous bornerons à une esquisse en grandes lignes des possibilités thérapeutiques qui sont apparues pendant cette période — ou qui ont déjà disparu entretemps.

Ne fut ce que pour accentuer le fait que l'on a déjà appris aussi à obtenir sans aucun doute des résultats sérieux sur le terrain de ce spécialisme qui est encore considéré parfois comme enfant pauvre de la médecine.

Déjà depuis l'Antiquité, on connaissait l'action sédative et somniférique du pavot et de l'opium, les effets de plantes solanacées comme la mandragore, la belladonne, la pomme épineuse et la jusquiame, des moyens végétaux comme l'aconite, la valériane et l'asa foetida (une gomme résineuse orientale).

Mais les premières matières chimiques pures pour le traitement de malades nerveux, n'ont apparu qu'en ce siècle précédent où débute notre aperçu.

Depuis 1857, des composés de brome sont employés contre les troubles sensoriels épileptiques et comme calmants généraux; ce sont les bromures de sodium, de potassium et d'ammonium, souvent prescrits en association mutuelle; un désavantage pouvait se trouver en quelques effets secondaires comme des troubles de la digestion ou des réactions cutanées (acné du brome).

Dans les asiles, des malades agités étaient aussi traités (depuis 1883) au produit chimique paraldéhyde, sous forme de solution ou même par voie anale (clystère).

Depuis 1868, on se servait souvent et en assez hautes doses de l'hydrate de chloral, comme calmant et comme somnifère, même pour enfants et pour vieillards; sous forme de sirop, il avait remplacé pour-ainsi-dire le laudanum (teinture d'opium).

Ce n'est qu'au début de notre 20e siècle que l'on apprend à appliquer un nouveau groupe de produits : les barbituriques, dont en premier lieu le Véronal ou barbital (1903), suivi du Luminal (phéno-barbital), du prominal (méthyl-phénobarbital) et quelques autres. Ces médicaments sédatifs trouvaient aussi, en de plus fortes doses, une indication contre l'insomnie et l'épilepsie.

Mais bientôt ils s'avéraient aussi aptes à pouvoir engendrer de l'accoutumance et de la dépendance, tandis que les tentatives de suicide aux barbituriques se multipliaient.

Depuis lors, le nombre de remèdes chimiques, presque tous synthétiques dorénavant, s'est accru en un rythme accéléré.

Tandis que l'on devait auparavant s'accommoder de moyens s'offrant dans la nature, selon une expérience séculaire, — on se lança maintenant dans l'invention et la création de formules complètement neuves. Ce fut le début d'une évolution très utile, mais en même temps, comme l'on constaterait plus tard, pas dépourvue d'un certain danger.

Il nous faudrait aussi dire ici quelques mots d'une série de thérapeutiques considérées comme assez brutales, ayant joué un rôle important en psychiatrie récente.

Déjà depuis l'Antiquité se retrouvent des essais en traitement de choc. Par un effet de surprise, un changement de conscience, ou même une intervention de force, on tentait de modifier l'état affectif ou émotif du malade, et d'améliorer ses idées. Au siècle précédent, de tels moyens furent repris, re-découverts, créés ou raffinés de sorte que l'on disposait maintenant de chaises tournantes et machines rotatives, d'installations de douche, de cures vomitives et purgatives, d'abcès de fixation au camphre ou à la térébenthine.

Certaines de telles méthodes nous paraissent maintenant trop brutales, mais l'intention était en tout cas positive — et le résultat obtenu souvent aussi (bien que le mécanisme de l'effet restait la plupart du temps assez vague).

A Gand, Guislain aussi a expérimenté avec de telles applications de choc : en ses premiers ouvrages, nous retrouvons plusieures planches explicatives concernant ces techniques; mais par après, il évolua vers une approche plus douce que nous appelerions maintenant "psychothérapeutique" : patience, attention et relation de confiance devaient jouer un rôle prépondérant ("faire du bien, beaucoup de bien au malade"); en ce point de vue, il fut certes un précurseur.

La série des nouvelles thérapeutiques de choc fut inaugurée par l'Autrichien Julius Ritter Wagner von Jauregg qui constata en 1917 que l'affection redoutée nommée "paralysie générale" pouvait être arrêtée par la provocation artificielle d'une fièvre malarique; une telle cure devait alors être coupée à la quinine. Ce traitement à la fièvre n'était pas sans danger pour des malades dont l'état général laissait à souhaiter ou dont le coeur était affaibli; mais c'était un progrès, vu que la complication nerveuse de la maladie vénérienne restait jusque là incurable et inévitablement fatale; — et la pénicilline n'apparaîtrait que beaucoup plus tard.

Cette P.G., suite tardive d'une syphilis non (ou insuffisamment) traitée, se rencontrait fréquemment dans tous les asiles (Esquirol p.ex. estimait même jusqu'à la moitié de ses aliénés comme appartenant à ce groupe).

Ce fut donc bien à juste titre que Wagner von Jauregg reçut le prix Nobel (1927) pour sa découverte.

Peut-être en lointaine réminiscence au traitement de sommeil au temple des anciencs Grecs, le Suisse Jacob Klaesi introduisa en 1922 la cure de sommeil à l'aide de barbituriques. Surtout par injection de Somnifène (un mélange de sels de l'acide barbiturique), des malades turbulents, agités ou anxieux restaient endormis jusqu'à trois semaines. Chaque jour, on les laissait reprendre légèrement connaissance afin de rendre possible l'alimentation et la toilette.

Un contrôle somatique rigoureux était nécessaire pour prévenir des complications comme une déglutition fautive, stase, infections et pneumonie éventuelle, le décubitus aussi (des escarres par alitement prolongé). Ce traitement entraînait donc de sévères exigences aussi bien pour l'assistance qu'au contrôle médical.

En 1933, le docteur autrichien Manfred Sakel créa la cure d'insuline pour le traitement de la schizophrénie débutante.

Cet hormone de la glande pancréatique, déjà connu comme ressource contre le diabète, fut administré maintenant en surdosage pour éliminer la conscience. Ceci pouvait être répété journellement, après quoi le malade était réveillé chaque fois de son état comateux par une solution de glucose introduite dans l'oesophage par voie de sonde. Quoique le mécanisme précis de l'influence ne fut jamais éclairé, cette méthode se manifestait quand-même comme la première arme utile contre la maladie redoutable : un tiers environ des cas initiaux de schizophrénie pouvaient être améliorés nettement à l'aide de cette cure. Il s'agissait néanmoins d'une méthode assez compliquée, et non dépourvue de risques.

L'année suivante, en 1934 donc, l'Hongrois Ladislas von Meduna appliqua le produit Cardiazol à fin psychiatrique; cette matière — du point de vue chimique le tétrazol pentaméthylénique — avait déjà trouvé son indication comme stimulant de la circulation, mais s'avéra aussi maintenant (en injection à plus forte dose) génératrice de convulsions épileptiformes. Un tel traitement de choc se montra salutaire pour certains cas sérieux (surtout maniaco-dépressifs), mais fut délaissé par-après comme engendrant trop de peur chez nombre de malades.

En 1937, les Italiens Ugo Cerletti et Lucio Bini mettaient à point une méthode qui avait été examinée d'abord chez des animaux : c'était l'électrochoc ou traitement à l'éléctroconvulsion, surtout indiqué chez la "psychose maniaco-depressive".

En principe, on laissait passer un voltage réglable, pendant une fraction de seconde seulement, par les lobes frontaux du cerveau, ce qui éliminait sur coup la conscience et provoquait une crise convulsive épileptiforme. Après quelques applications (p.ex. trois fois par semaine), l'humeur troublée se normalisait assez vite; ceci ne signifiait pas que la disposition maniaco-depressive se modifierait (elle se manifeste souvent comme plus-ou-moins constitutionnelle, comme l'avait déjà présumé Emil Kraepelin et comme l'affirmerait par-après Ernst Kretschmer), mais tout-de-même que l'on pouvait dissiper la bouffée maniaque ou la dépression mélancolique.

Quelques précautions étaient à prendre pour éviter des complications éventuelles : le patient devait être examiné afin de dépister une possible contre-indication somatique à un tel traitement; lors de l'application même, des lésions de la langue ou des ruptures musculaires devaient rester évitées; à cette fin, un relaxant musculaire comme le curare pouvait être utilisé.

Quoique l'éléctrochoc obtint un mauvais renom (surtout par l'abus de certains aliénistes qui l'ont appliqué à tort et à travers) — il reste un fait qu'avec cette méthode on a retenu du suicide et sauvé d'innombrables malades dépressifs.

Dans les années '50, les produits psycho-pharmaceutiques furent introduits, dont bientôt aussi une catégorie spéciale nommée thymoanaleptique, p.ex. l'imipramine (Tofranil) et l'amitryptyline (Tryptizol); ces produits rectificateurs de l'humeur triste ont depuis lors rattrapé et supplanté presque totalement l'électrochoc.

Un dernier traitement appartenant en quelque sorte au groupe des thérapeutiques de choc, est la "psychochirurgie" (on parle aussi de leucotomie ou lobotomie). Après les essais du Suisse Rudolf Burckhardt (1891) et de l'Esthonien Ludwig Puusepp (1910), le Portugais Egas Moniz développa en 1936 la méthode opérative selon laquelle un nombre de fibres nerveux des lobes frontaux est interrompu; de cette façon, les symptômes aigus de schizophrénie résistante ou de névrose obsessionnelle maligne peuvent être atténués.

Dans les années après la seconde guerre mondiale, cette technique a surtout été appliquée par les Américains Walter Freeman et James Watts; on en a même abusé, jusqu'à ce que l'intervention fut abandonée à la fin, surtout vu le risque d'endommager la personnalité du malade.

La construction et les fonctions précises du cerveau humain ne sont en effet pas encore suffisamment connues pour permettre une section (le plus souvent aveugle). Il s'agit aussi d'une intervention irréversible: si le résultat obtenu est décevant, on ne peut plus revenir sur ses pas.

A côté des thérapeutiques somatiques, des traitements psychiques se sont annoncés aussi en la seconde moitié du siècle précédent; ils entrent surtout en ligne de compte pour les troubles mineurs nommés névroses.

En ce temps, l'école de Nancy p.ex. (avec Ambroise-Auguste Liébault et Hippolyte Bernheim) s'appliquait à l'étude de l'hypnose. On essayait de procurer une base scientifique aux observations et épreuves de l'Autrichien Franz-Anton Mesmer, qui avait travaillé vers la fin du 18ᵉ siècle à Vienne et à Paris avec l'influence du soi-disant magnétisme animal. Ce qui apparaîtrait par-après comme de la psychothérapie suggestive.

Le pharmacien français Emile Coué cherchait de la guérison par une méthode d'autosuggestion, se basant sur le principe qu'une idée — pourvu qu'elle soit répétée suffisamment — tente à se réaliser.

Le traitement à la persuasion (Paul Dubois, Berne, début de notre siècle) s'efforçait à faire disparaître les plaintes du malade par influence et conviction suggestives.

Après des études sur l'hystérie et son traitement éventuel par le neurologue Jean-Martin Charcot à la Salpêtrière de Paris, un de ses disciples le psychiatre Pierre Janet y impliqua aussi une série d'autres névroses.

Mais ce fut surtout la "psychologie des profondeurs" qui fournirait, avec la psychanalyse, l'explication et le traitement les plus connus des troubles névrotiques; ceci vers la dernière transition de siècle.

Probablement inspiré par des idées du professeur à Dresde Carl-Gustav Carus (1789-1869) — un humaniste qui était aussi bien savant (médecin et psychologue) qu'artiste (poète et peintre), et qui publia en 1846 "Psyche, zur Entwicklungsgeschichte der Seele" dans laquelle nous trouvons déjà de remarquables opinions comme "La clé à l'explication du psychisme conscient se trouve dans l'inconscient", — l'Israëlite viennois Sigmund Freud, qui avait d'ailleurs assisté aussi bien à l'école de Nancy qu'à celle de Charcot, élabora, en collaboration avec le médecin Jozef Breuer, ce que l'on appelle depuis lors la psychologie des profondeurs ou psychologie dynamique. (Le professeur d'Utrecht Rümke p.ex. se déclare convaincu que l'oeuvre citée de Carus contenait déjà tout le fondement de la thèse ultérieure de Freud).

Freud et Breuer étaient d'avis qu'un fond caché pour les troubles névrotiques était à chercher dans les évènement choquants vécus pendant les premières années (traumatisme psychique) ou des penchants sexuels refoulés.

Ramener en connaissance ce qui restait refoulé par la conscience (au moyen d'idées spontanées et associations, et d'explication des rêves), discuter les conflicts et les complexes, résoudre les problèmes cachés et les tensions internes, tout cela peut agir de façon purifiante (catharsis), soulageante, guérissante.

Le désavantage majeur de la méthode psychanalytique réside dans le fait que seulement peu de cas sélectionnés n'entrent en ligne pour ce traitement : ils doivent être suffisamment intelligents et développés, disposer d'assez de patience et d'introspection, et aussi d'un vocabulaire assez riche pour pouvoir verbaliser la matière.

Une telle cure peut durer très longtemps (des années..), prendre beaucoup de temps et amener des frais considérables (vu que les mutuelles p.ex. n'y interviennent pas). Tout ceci y comporte que la psychanalyse soit restée un traitement plus ou moins élitaire.

Un des collaborateurs les plus proches de Freud, Alfred Adler, choisit lors de sa rupture en 1911 pour sa propre "Individualpsychologie" où il vit la force motrice capitale non tellement en sphère érotique mais plutôt dans le penchant à se faire valoir ou la passion du pouvoir. C'est par des frustrations en ce domaine-là que les névroses seraient déterminées; et le traitement devait surtout viser une meilleure adaptation et insertion sociale.

Un autre représentant important de la psychologie des profondeurs, le Suisse Carl-Gustav Jung, apporta encore une autre vision : l'homme deviendrait névrotique en n'aboutissant pas à un épanouissement suffisant et équilibré; la thérapie doit avoir en vue une espèce de rééducation ou réédification en personnalité plus harmonieuse.

Chaque tendance — dont seulement les trois plus importantes sont nommées ici — a developpé ses propres moyens analytiques de traitement.

Au cours des années, l'eventail des possibilités psychothérapeutiques s'était donc élargi : des méthodes couvrantes (rassuration, encouragement, persuasion, suggestion, hypnose) aux méthodes découvrantes, exploratrices ou analytiques, avec toutes leurs variantes.

Comme appartenant au premier groupe, on pouvait encore ajouter le "training autogène" de l'Allemand J.H. Schultz (depuis 1932), appelé aussi auto-relaxation concentrative, et la "logothérapie" (littéralement : traitement par le dialogue) de Viktor Frankl (école viennoise). La seconde catégorie contenait encore la "narcoanalyse" au moyen d'une injection intraveineuse lente et dosée du barbiturique pentothal; pendant l'état de sémi-sommeil, ainsi obtenu, on pouvait aussi aboutir à une "catharsis" soulageante et libérante. Toute cette série de techniques psychiques était naturellement destinée en premier lieu au traitement des troubles névrotiques. Dans les asiles, où résident des cas plus malades, c.à.d. psychotiques, ces méthodes trouvaient généralement peu de résonance et d'application.

Comment avait évolué entretemps la situation dans ces asiles ? Dans la plupart des pays de l'Europe occidentale, le nombre d'institutions psychiatriques s'accroissait. Elles remplaçaient les "maisons de fous" antérieures. Dans ces instituts — au cas des bâtiments nouveaux, maintenant en dehors des villes — on disposait enfin du volume nécessaire; aussi de médecins spécialisés, ainsi que de personnel formé, appartenant souvent à des ordres ou congrégations religieux. On pouvait dorénavant parler vraiment d'hôpitaux. Des hôpitaux spéciaux alors, vu qu'il s'agissait d'instituts fermés aux malades colloqués.

L'opinion selon laquelle les aliénés soient des malades, fut encore accentuée par les soins sous alitement, propagés surtout par le clinicien allemand Clemens Neisser à la fin du siècle passé. De cette façon, plus d'attention aux malades pouvait être portée par les médecins et le personnel soignant. L'examen et l'observation en étaient favorisés. Des malades tourmentés, épuisés, exténués pouvaient regagner en forces. L'apaisement corporel pouvait aussi profiter à l'esprit. La manière de porter des soins signifiait déjà un traitement en soi-même.

Après un certain temps néanmoins, un désavantage se déclara aussi lié à cette méthode. Un alitement systématique favorise l'oisiveté, l'ennui et l'hébètement. Un séjour au lit trop prolongé peut conduire, surtout chez des malades corpulents et immobiles, au décubitus (escarres). Un manque de mouvement corporel et de ventilation pulmonaire favorise des infections comme la tuberculose. La phtisie des poumons se rencontrait assez fréquemment dans les asiles, où l'on trouvait p.ex. des malades négativistes enroulés comme des hérissons sous leur draps ou couverture.

Une méthode appliquée en nombre d'asiles psychiatriques — surtout pour malades agités — pourrait être appelée balnéothérapie.

L'expérience avait appris (déjà depuis l'Antiquité) que des bains tièdes ont un effet relaxant et calmant. Surtout à partir du début de notre siècle, certains instituts y faisaient systématiquement appel. Des patients agités pouvaient rester pendant des journées (ou même des semaines) dans un bain tiède, clôturé par une voile ou bâche, parfois aussi par un couvercle de planches fermant autour du cou.

Un inconvénient restait le fait que la peau de la paume de main ou de la planche de pied pouvait s'émollier et se détacher. Il y avait aussi le risque d'un eczème-de-bain ou de mycoses. De telles complications pouvaient être contrecarrées en couvrant le malade d'abord d'une couche de vaseline ou d'une autre substance graisseuse et hydrofuge.

D'autres applications d'hydrothérapie étaient des douches, des ablutions, des enveloppements. En ce dernier cas, le malade était enrôlé en un drap mouillé, cloisonné encore par une bâche. Ici aussi, l'intention était de calmer. Mais on pouvait considérer aussi ce moyen comme une espèce de contrainte.

La véritable camisole de force pour malades difficiles, était un vêtement en matière solide et rude, aux manches longues qui pouvaient être nouées afin de restreindre la mobilité de la personne en question.

Des patients agités étaient plaçés en une cellule d'isolation. C'était souvent une "chambre bleue", dans l'espoir qu'une couleur bleue-pâle introduirait de la détente.

Chez des malades refusant la nourriture, on pouvait se voir obligé d'administrer une alimentation liquide par sonde nasale; ceci exigeait alors beaucoup du personnel soignant.

Déjà Guislain attachait beaucoup d'importance à une thérapie par le travail et l'occupation. Ainsi il nous rapporte p.ex. qu'entre ses environ deux cents malades de l'asile gantois pour femmes, dont il reçut la responsabilité en 1828, il n'y en avait pas dix qui n'étaient pas occupées toute la journée d'une façon utile. A l'étranger aussi, quelques pionniers ou esprits éclairés prônaient déjà cette méthode ou l'appliquaient comme traitement au siècle passé.

Mais ce fut alors surtout l'Allemand Hermann Simon qui en accentua encore plus fortement l'importance en 1926 avec sa "thérapeutique-plus-active" à Gütersloh (Westphalie).

La notion et le terme d'ergothérapie reçurent peu à peu droit de cité; et à plus grande échelle on allait admettre qu'une mise à l'oeuvre peut soigner pour distraction, sentiment d'utilité et de responsabilité, confiance en soi, rééducation.

Encore un pas plus loin nous amena à la thérapie créative. L'auto-expression peut offrir des possibilités d'amélioration ou même de guérison. Des centres progressistes n'installèrent non seulement des ateliers où la productivité s'associa à l'ergothérapie, mais créèrent aussi tout un éventail de chances pour récréation, sports et jeux, traitement par le mouvement, excursions, théâtre, musique, chant et dance, expression libre et auto-découverte.

Au cours des années, on a vu apparaître, surtout après la seconde guerre mondiale, des sections ou des instituts psychiatriques du type ouvert, où il n'y avait donc plus question d'intervention justicielle ou politionelle comme c'était le cas dans la collocation classique.

On assistait aussi à un changement des dénominations : tandis que beaucoup d'asiles étaient devenus hôpital ou institut, nombre de départements ouverts reçurent maintenant l'étiquette de maison-de-repos. Le centre allait être ouvert maintenant aussi à des personnes névrotiques qui pouvaient y venir passer une cure.

La contrainte à l'enfermement s'affaiblissait donc, l'autorisation officielle tombait de plus en plus en désuétude. Mais aussi dans les instituts même, beaucoup de moyens de coercition tendaient à disparaître. En application du système de "no-restraint" prôné par Conolly, la camisole de force et le masque s'effaçèrent de plus en plus; de même pour la cellule d'isolation et les bains prolongés calmants.

Les grandes grilles et les murs fermés allaient faire place à des haies, des parterres de fleurs. On s'efforçait à donner à l'asile un aspect moins inquiétant et plus aimable.

Mais l'atmosphère se transformerait surtout dans les années '50. Par l'introduction des produits psychotropes ou médicaments de l'esprit (les dérivés de la phénothiazine, type Largactil, et par-après les butyrophénones, type Haloperidol), l'agitation disparaissait plus ou moins; une série classique de symptômes aigus et troublants pouvaient être éliminés des sections. Plus de malades pouvaient participer dorénavant à l'ergothérapie. Cellule, chambre d'isolation et bain continu devenaient pour-ainsi-dire superflus.

Nombre de patients aussi ne devaient plus rester maintenant à l'asile comme cas devenant chroniques. Ils pouvaient sortir après une cure de traitement plus-ou-moins intensive, les uns guéris, d'autres améliorés et de nouveau admissibles du point de vue social. On pouvait parler d'un plus grand transit dans les instituts.

Sans aucun doute, les nouveaux moyens chimiques signifiaient un gain remarquable et une borne; aussi longtemps naturellement qu'il n'en soit pas abusé comme d'une nouvelle "camisole de force chimique", et que l'on ne perde pas de vue qu'ils présentent aussi des inconvénients et des activités secondaires.

Après les diverses méthodes de choc, on était arrivé maintenant sans aucun doute en une phase pharmacothérapeutique de la psychiatrie; pour combien de temps, nous l'ignorons encore; le temps l'apprendra.

Comme nous voulions parler ici en grandes lignes d'un siècle de psychiatrie seulement, c.-à.-d. d'environ 1850 à 1950, des considérations sur le proteste plus récent de la part de l'antipsychiatrie n'entrent plus en ligne; et il suffit peut-être de constater ici que ce mouvement s'est déjà apaisé entretemps, — bien qu'il en reste tout-de-même quelque chose : notamment qu'on doive tenir plus compte des aspects et facteurs sociaux, et qu'on évolue des grands instituts-monstres vers des centres à moins-grande échelle.

En conséquence des progrès thérapeutiques en psychiatrie, de si grands asiles ne sont d'ailleurs plus nécessaires; tandis que les malades schizophrènes p.ex. (qui y forment encore toujours la majorité des habitants) restaient auparavant longtemps ou même définitivement en hospice, ils ne sont hospitalisés maintenant que pour une cure relativement courte et intensive.

En ce coup d'oeil sur l'évolution de la psychiatrie,le progrès en ce domaine paraît peut-être ne pas été aussi spectaculaire que dans l'extermination de maladies infectieuses ou dans la transplantation d'organes, mais endéans la courte durée de son existence comme science — courte dans le cadre de toute l'histoire, notamment environ un siècle — elle a tout-de-même déjà atteint l'un et l'autre.

Naturellement, elle se trouve encore toujours pleinement en route, dans un voyage assez difficile, il reste encore beaucoup d'ouvrage, ne soit ce que concernant cette schizophrénie encore toujours si mystérieuse, que l'on peut déjà freiner ou endiguer maintenant, mais ne pas encore guérir parce que personne sur terre n'en connait encore la cause précise. D'importantes découvertes nous attendent donc encore toujours, comme Eug. Carp le présume en son livre "Psychiatrie future".

Encore plus peut-être que pour toute la médecine, il reste entretemps en vigueur pour notre branche, ce que le père de notre science constata déjà il y a si longtemps en ses "Aphorismes" (et ce que l'on comprend peut-être encore mieux que jamais en achevant une carrière) : Ars longa, vita brevis; la vie est courte, la science demande beaucoup de temps; l'occasion est fugitive, l'expérimentation dangereuse, le jugement difficile.

Prof. em. Dr. A.K. Evrard;
Gent - Gand.

LAUDATIO

L.J. Vandewiele

Als collega proximus heb ik de eer, mede in naam van de dekaan van de Fakulteit van de Farmaceutische Wetenschappen Prof. Dr. A. De Leenheer, hier Prof. Dr. H.A. Bosman-Jelgersma te mogen inleiden.

De Fakulteit van de Farmaceutische Wetenschappen heeft tijdens haar zitting van 6 april 1989 unaniem voorgesteld, om de Sarton-medaille tijdens het Academiejaar 1989-1990 toe te kennen aan Mevr. H.A. Bosman-Jelgersma, hoogleraar in de geschiedenis der Farmacie aan de Rijksuniversiteit te Leiden.

Henriëtte Augusta Jelgersma werd geboren te Oegstgeest, studeerde aan de Rijksuniversiteit te Leiden, waar zij in 1956 het apotekersdiploma behaalde. Van 1951 tot 1957 was zij hoofdassistent op het laboratorium om gerechtelijk en toxicologisch onderzoek te Leiden en is daarna gedurende 23 jaar als officina-apoteker werkzaam geweest. Zij trad in het huwelijk met Apoteker K. Bosman, eveneens titularis van een apoteek.

Mevr. Bosman-Jelgersma promoveerde in 1979 tot doctor aan de Vrije Universiteit te Amsterdam op het proefschrift : "Vijf eeuwen Delftse Apothekers". Haar promotor was de beroemde Prof. Dr. G.A. Lindeboom.

In 1983 werd zij benoemd tot bijzonder hoogleraar in de geschiedenis der Farmacie aan de Rijksuniversiteit te Leiden. Bij de aanvaarding van het leerambt sprak zij een merkwaardige rede uit : "De geschiedenis van de Farmacie : een terugblik in bewondering". Prof. Bosman-Jelgersma heeft heel wat publikaties op haar naam staan, waarvan misschien wel het meest bekende en meest populaire rijkgeïllustreerde boek : Poeders, Pillen en Patiënten. Apothekers en hun zorg voor de gezondheid door de eeuwen heen.

Daarbenevens vernoem ik zonder volledig te willen zijn haar activiteiten : de jaarlijkse organisatie van de Farmaceutische Historische Dag; haar bemoeiingen voor de Kring van de geschiedenis van de Pharmacie in Benelux en het Genootschap voor de geschiedenis van de Geneeskunde, Wiskunde, Natuurwetenschappen en Techniek en als medeorganisator en/of voordrachtgever op talrijke evenementen die met de geschiedenis der wetenschappen te maken hebben.

Wat echter vooral de keuze van Prof. Bosman-Jelgersma voor het verwerven van de prestigieuse Sarton-medaille wettigt, is naast haar verdienste als hoogleraar in de geschiedenis van de farmacie, haar enthousiasme waarmede zij bij haar studenten de interesse voor haar vak tracht waar te maken en de promovendi begeleidt.

Ik wil hiermee besluiten en Prof. Dr. H.A. Bosman-Jelgersma verzoeken het woord te willen nemen, over : Het farmaceutisch erfgoed van de Nederlanden.

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THE PHARMACEUTICAL HERITAGE OF THE NETHERLANDS

Prof. Dr. H.A. Bosman - Jelgersma

With the realization of a Europe without boundaries, which most associate with the magical year of 1992, and which surely must signify much more than a mere joining together of nations, it is worthwhile to examine the past and see along which paths the pharmacy of the Southern and Northern Netherlands developed; paths which were sometimes shared by both and at other times diverged. Contemporary pharmacy is founded on a common heritage, which took shape over the centuries.

It is therefore useful to review a number of historical facts which affected the practice of pharmacy in the Netherlands.

At the end of the Middle Ages, the Netherlands formed part of the great Habsburg Empire of Charles V, who often resided at Brussels and initiated a significant centralization process. In the 16th century these '17 United Netherlands' revolted against the Spanish-Habsburg rule. The centre of rebellion in the South was the resistance against Phillip II, which began with the iconoclastic outbreak in 1566. But unity, so splendidly depicted by the 'Leo Belgicus' map in 1559, was destroyed after 1578 by the secession of the North.

As the 'Republic of the 7 United Netherlands', the North enjoyed considerable economic prosperity and cultural affluence well into the 18th century, especially after the fall of Antwerp in 1585, when many Southern refugees made new lives in the Republic. These immigrants brought with them their energy, capital, skills and commercial ties, qualities which had made the South so great.

Before the outbreak of the Eighty Years' War, Southern towns such as Brussels, Ghent, Leuven, Bruges and Antwerp had been far more prominent than those in the North. The emigration, however, caused a serious economic crisis in the South.

So Antwerp, which in 1560 could boast a population of 100,000, had but 40,000 inhabitants in 1590, and its flourishing herb and spice market was shifting little by little to Amsterdam.

Until 1713 the South remained under Spanish domination, when it fell under Austrian rule. In 1795 these 'Austrian Netherlands' were annexed by France and subjected to French legislation. In the North the 'Batavian Republic' came into existence after the arrival of the French. After 1806 French influence in the 'Kingdom of the Netherlands' gradually increased, particularly after the annexation by France in 1810. As in the Southern Netherlands everything was done along French lines.

After the liberation in 1813 North and South were united in the 'United Kingdom of the Netherlands' over which the Netherlands King William I assumed sovereignty. From the start this reunification stood little chance of success. Barely 16 years later, in 1830, the Netherlands and Belgium separated and became independent countries.

Following this brief historical introduction, let us go back in time to get an impression of the pharmaceutical heritage of the Netherlands. We will concentrate on the 16th and 17th centuries, in which ordinances were issued, books of prescriptions were published and sciences such as botany and chemistry came to be developed. This was all of enormous importance to the practising pharmacist.

It began long ago with the 'Constitutiones', issued by Frederik II von Hohenstaufen for the medical profession in 1240, in which guidelines were laid down for an independent and protected pharmacy practice. So in the Netherlands the first pharmacists set up practice from the 13th century.

The independence of these pharmacists demanded that guidelines, inspections and ordinances were established in accordance with which the profession was to be practised. The oldest pharmaceutical ordinance in the Netherlands was issued around 1300 at Ypres, a town then just as important and well known as Paris.

Later, regulations in the fields of medicine and dispensing were promulgated in the very affluent Southern Netherlands towns of Bruges, Ghent, Leuven, Brussels and Antwerp. At that time there were only a few pharmacists established in the Northern Netherlands, and it was not until the beginning of the 16th century that local pharmaceutical ordinances became effective in places like Maastricht, Amsterdam, Delft and Bergen op Zoom. A study of the texts of these ordinances shows that the Southern Netherlands regulations served as a model for those of the Northern Netherlands (1).

About 1300 a number of important basic principles for the practice of the pharmacy profession were laid down in the 'Keure van Yper' (2). A pharmacist was required to take an examination and swear an oath. The 'Antidotarium Nicolai', a book of prescriptions which had originated from Salerno, was declared binding. It is obvious then that another prerequisite was that the pharmacist or his assistant had to be able to read.

The 'Ordonnancie politique nopende het verkoopen van medicynen' (3), promulgated one and a half centuries later on 16th October 1456 at Ghent is, according to its modern publisher Leo Vandewiele, one of the oldest pharmacy ordinances which sets out fundamental principles for the practice of the profession. This ordinance served as a model for later regulations. Southern Netherlands towns had been in the lead as far as the development and execution of these local regulations was concerned. Their great economic strength in various areas gave them the edge over the Northern Netherlands towns.

Interesting too is the 'Placcaert op 't stuck der medecyne' (4), which was issued by the Emperor Charles V on 8th October 1540 at

Brussels. For the most part this edict resembles the 'ordonnacie' of Ghent which was published a century earlier.

What is important is that although this proclamation was issued at Brussels, it was intended for 'all the provinces of the Netherlands'. It was a national ordinance which fitted exactly with Charles V's centralization policy, and can be regarded as the first central regulation of pharmacy in the Netherlands. This decree could have had great infuence if the regulations and special tribunal it promised had been forthcoming.

This official document originated in a time of renewal and rebirth — 'Renaissance' which, under the influence of Italy, also manifested itself in the Netherlands.

In the Netherlands, scientific unfluence emanated mainly from the university town of Leuven, while administrative decisions were taken in Brussels, and economic and cultural development was concentrated in the towns of Bruges, Ghent and Antwerp. The Northern Netherlands were actually still appart of the outlying provincies of Europe. The North Netherlands humanist, Desiderius Erasmus (1466-1536) often stayed in Antwerp. Most of his books were published there by the famous printer, Michiel Hillenius van Hoogstraten, including his oration 'Lof der Geneeskunst' (Encomium artis medicae). This he dedicated in 1518 to his friend, 'insigni Medico', the accomplished physician from Lier, Dr. Henricus Afinius (5). Erasmus had this to say about medicines :

"There are so many differences between so many thousands of herbs, each growing in a different place, not to mention the rest of the medicines. And so much extensive study is necessary to be able to extract from all of the herbs, bushes, trees, animals, precious stones and even from poisons, curative medicines for all human ailments".

He refers to the range of medicines in the late Middle Ages, for which at least 80% of the medicinal materials were derived from plants. Botanical knowledge of these medicines was primarily based on 'De Materia medica' in five volumes by the Greek physician Dioscorides (55 A.D.).

During the Renaissance Dioscorides' work enjoyed considerable esteem. For a long time it served as a model for later herbals, in which simple botanical materials, the 'simplicia', were described.

A printed book which described and illustrated medicinal plants, a 'Herbarius', was published for the first time in Europe in the Netherlands. Of the edition in Netherlands, the 'Herbarius in Dyetsche', three Southern Netherlands publications are known, one from Leuven in 1484 and two from Antwerp in 1500 and 1511. The illustrations which appear in these books, however, show little resemblance to their natural counterparts. This made the identification of herbs difficult.

This changed a lot during the renaissance. The illustrations in the herbals of the three German 'fathers of botany', Brunfels, Bock and Fuchs, had already improved and were truer to nature. The work of the physician and humanist Leonhard Fuchs was especially impressive and indisputably superior to those of his predecessors Brunfels and Bock.

In his book 'Six Wings : Men of Science in the Renaissance', Sarton adds Valerius Cordus (1515-1544) to the three influential German botanists (7). Correctly, he thinks that Cordus surpassed the others in his botanical research. This young German physician wanted to study plants in their natural habitat before he described them.

Cordus travelled a lot and was the first to take the initiative in organizing botanical excursions for medical students. Botany was, after all, a supporting science to medicine. He also took knowledge of the simplicia in a totally different direction by introducing, alongside theoretical academic tuition — 'Lectura simplicium' — the practical demonstration : 'Ostensio simplicium'(8).

With his father — Euricius Cordus — a humanist, physician and botanist and his uncle a pharmacist, Valerius Cordus was involved with the materia medica from childhood. Alexander Tschirch (1856-1939), the well-known German pharmacognosist, even includes him among the 'fathers of pharmacognosy', together with Monardus and Clusius.

Although Cordus' materia medica is still firmly rooted in the Middle Ages, we can already see the spirit of the new age, the Renaissance, in his botanical research, where he described countless new and rare plants.

In the field of practical dispensing Cordus created order out of the chaotic state that this occupation was then in (9). In 1534, encouraged by his uncle who was a pharmacist at Leipzig, he began to compile a book of prescriptions, which included a number of standardized preparations. This 'Dispensatorium' testifies to his profound practical pharmaceutical knowledge and possesses great scientific value, because Cordus, led by personal observation and research, not only described the characteristics features of nearly 225 different simplicia, but also noted the origin of raw materials and possible adulterations.

Unfortunately, Valerius Cordus died in 1544, not yet 30 years old. After his death, in 1546, the 'Dispensatorium' was published at Nuremburg and became the first official pharmacopoeia in Germany.

For the practising pharmacists in the Netherlands, this book of prescriptions was to become exceptionally important.

In the Southern Netherlands, the followers of the German botanists were Dodonaeus, Clusius and Lobelius, who during the Renaissance wrote important works in which a systematic classification and detailed description of many plants can be found.

These Flemish botanists became famous, but would never really have won recognition without their publisher, Christoffel Plantijn (10).

Partly thanks to him an important part of this pharmaceutical heritage has remained intact. In 1548 Plantijn came from Paris to Antwerp, the most important commercial town north of the Alps, and a centre of humanism and science.

No less than 66 printers of books were at work there, and Plantijn started his printer's 'De Gulden Passer' in 1555. This firm became one of the most important publishers in the Netherlands. Plantijn had scientific sympathies, and he was interested above all in the development of the natural sciences, especially botany.

It was just at this period that much research was being done on new material that had been brought back from long journeys to other parts of the world, and which had to be examined, described and illustrated.

Among these were a large number of medicines which until then were completely unknown here, such as Kina, ipecacuanha, sarsaparilla and tolubalsem. The Flemish botanists contributed greatly to the knowledge of these medicines.

The 'Cruyde-boeck' (11) by the physician and botanist Rembert Dodoens, which appeared in 1554, had an enormous influence on practical pharmacy.

Dodoens gave details of origin, collection, preservation, natural features, smell, taste, colour and other specific characteristics of a large number of simplicia. These are what we would refer to today as 'quality requirements'. It removed much of the insecurity that pharmacists often had concerning the processing of the 'opregte simplex'. More than anything the true to nature illustrations in this Cruyde-boeck were of great value. Moreover, the book was not written in Latin, but in the 'ghemeyne Neerduytse tale' (common Dutch language), so that anyone could consult it.

The Antwerp humanist, Carolus Clusius (12), known as the wisest man of his time, was the first to describe the flora of particular regions such as Spain, France and Austria. In addition, being the polyglot he was, he translated botanical works of other authors into Latin.

He translated the Spanish books of Da Costa and Monardus, and the Portuguese works of Garcia D'Orta, and so doing contributed to a growing knowledge of medicines from other parts of the world.

Clusius maintained close relations with pharmacists, especially with those who possessed their own herb gardens. They corresponded on exotic plants and exchanged botanical material. His friend, the Antwerp pharmacist Peeter van Coudenberghe, urged him to translate the Italian antidotarium 'Ricettario utilissimo' which appeared in Venice in 1560. Plantijn published Clusius' translation in 1561 (13).

In 1581 the 'Kruydtboeck' by Mathias de L'Obel (Lobelius) came off the Plantijn presses (14). Lobelius too had connections with various pharmacists, whom he mentions by name in his 'Kruydtboeck'. He elaborates on his friendship with the pharmacist Peeter van Coudenberghe, whose garden he considered to be the richest, most well-tended in the world. In 1548 this Antwerp pharmacist planted a herb garden of two hectares, which became one of the sights of Antwerp famous throughout Europe, not least for its exotic plants derived from Africa, Asia and America (15).

Dodonaeus, Clusius and Lobelius frequented Van Coudenberghe's garden and respected him as a scientist and scholar. Just as Cordus stands in the line of the German botanists, so Van Coudenberghe can be counted among the outstanding Flemish botanists of the Renaissance.

Plantijn asked Van Coudenberghe to thoroughly revise and supplement Valerius Cordus' 'Dispensatorium', because he wanted to publish it. This 'Dispensatorium', which came out at Nuremburg two years after Cordus' death, had not been edited by Cordus himself. Plantijn, who recognized the great value of this work, rightly feared that the 1546 edition would no longer suffice. Hence his request to Van Coudenberghe who supplied the 'Dispensatorium' with comments and corrected more than 400 inaccuracies. The book was published by Plantijn in 1568.

The great influence that Cordus' 'Dispensatorium' had in the Netherlands is evident from the numerous reprints, including several Dutch translations. The 1614 translation, entitled 'Den Leydsman ende onderwyser der Medicynen', was completely revised by Lobelius.

Because Cordus' book of prescriptions was entirely based on the classical, ancient Arab medicine and pharmacy, it mentions nothing of the chemical medicines that were propagated in the early 16th century by the Swiss physician Paracelsus. Paracelsus, who was both maligned and applauded, roamed all over Europe, visiting battlefields, universities and hospitals to gain experience (16).

So in 1519 he came to Antwerp and visited the market for herbs, spices and new, often exotic, medicines. He wrote that here he had learned more than at all the universities he had visited. Paracelsus frequently worked with mercury, antimony, arsenic and iron compounds. This led to new insights into medicine and the preparation of medicines. Pharmacists began to prepare medicines in their own laboratories.

Paracelsus' ideas for reform were further developed by others, and propagated as 'iatrochemistry'. In 1650 iatrochemistry reached its peak in the Northern Netherlands.

In the North, to which many Southern Netherlands had emigrated after the fall of Antwerp in 1585, Amsterdam became an international centre for trade and culture within a few decades (17). The flourishing Antwerp herb and spice trade shifted to Amsterdam, because many Southern Netherlands spice and herb merchants had moved there.

In Leyden, the intellectual bulwark in the liberated area, where in 1575 the Leyden univerity was established by Prince William of Orange, the population doubled between 1580 and 1610 to 30,000, and the number of pharmacies increased from 5 to 10. Round about 1620, 67% of the Leyde population was Southern Netherlands.

This mass emigration was not solely the results of religious difficulties : it was also occasioned by the very serious economic crisis which originated in the South. Not only did confectioners, herbalists, teachers, printers and carpet weavers leave, but also scholars, after the Leuven university began to decline. After all, isn't prosperity in a way also necessary for scientific study and growth ?

Furthermore, the curators of the Leyden University went to all lengths to attract famous scholars, such as the Leuven humanist Justus Lipsius in 1578, who was dubbed the second Erasmus. In 1582 Dodonaeus came to Leyden on account of his appointment as professor of medicine, and in 1593 Clusius became professor of botany at the University of Leyden. By 1578 Lobelius already resided in Delft, where he was court physician to prince William of Orange, to whom he dedicated his 'Kruidtboeck', published in 1581.

Plantijn had also emigrated to the North for economic reasons. It was probably a well-considered move on his part in order to gain control of the Northern Netherlands book trade (18). In the Spring of 1583, still prior to the fall of Antwerp, he opened his 'Officina Plantiniana' at Leyden. On 14th May 1584 he was appointed as university printer, and thus Leyden acquired a scientific publisher, a development which marked the beginning of an age-old tradition.

Although Plantijn had many friends in Leyden — Lipsius, Dodonaeus, Douza and Jan van Hout, the latter two curator and secretary of the university respectively — he still returned to Antwerp after its fall. He left his Leyden business in charge of his son-in-law, Frans van Raphelingen.

Among the numerous publications which saw the light of day through this establishment from 1583 to its closing in 1619, were a number of pharmaceutical works (19).

Besides the books on chemistry, alchemy and pharmacology, the writings of Paracelsus, Fuchs, Clusius and Dodonaeus above all supplied the large demand from practising pharmacists for books on prescriptions. These were the works of Cordus, Jacobus Sylvius, Renodaeus and Augsburg's pharmacopoeia, to mention but a few. These prescription books had a great influence on the composition of the Northern and Southern Netherlands town pharmacopoeias, which had been published since 1636, beginning with that of Amsterdam. When the trading relations between the North and South gradually became more difficult as a result of the war, the Leyden publishing house set up by Plantijn in the 'Republic of the 7 United Netherlands' contributed considerably to the spread of these pharmaceutical manuals.

Despite the fact that many of the Flemish intelligentsia emigrated to the Northern Netherlands, the South did retain some of its appeal. Plantijn went as quickly as possible to Antwerp once the peace was somewhat restored. Lipsius, the Leyden 'Lumen academiae', returned to Leuven in 1592.

In 1594 Clusius wrote from Leyden to his friend Lipsius : "If I'd known that this would happen, I never would have set foot here" (20). Clusius was already 66 years old when he was appointed by the University of Leyden to supervise the setting up of a Hortus botanicus.

Owing to invalidity, he was unable physically to do the job and so a deputy was appointed, the Delft pharmacist Dirk Cluyt, who in a short time laid out and planted the university garden.

Until his death in 1609, Clusius held only an honorary position at Leyden university, free of all duties. He devoted himself entirely to the publishing of his collected works and to his voluminous correspondence with many of his acquaintances, especially international ones. Because of his great interest in exotic plant products which he came across in pharmacies, he never passed up an opportunity to procure these.

Thus in 1601 he wrote a 'Memorie', which the commanders of the ships that sailed to Africa and the East Indies were to pass on to the ships' pharmacists and surgeons. It stated which plants, fruits and seeds had to be taken along on the journey (21). Dodonaeus lived in Leyden for only a short period. He died in 1585 at the age of 68, just three years after his arrival.

Following the death of Prince William of Orange in 1584, Lobelius was appointed town physician of Middelburg. From 1596 until his death in 1616, Lobelius lived in England, where he supervised of a medical herb garden.

In the 16th-century there was still no university garden in the Southern Netherlands. It did, however, have the pharmacist Peeter Van Coudenberghe's private garden, mentioned earlier, which was visited by renowned botanists such as Garcia d'Orta and Conrad Gesner (22).

During the siege of Antwerp Van Coudenberghe's life's work was destroyed overnight. He died around 1599. By then the Leyden Hortus botanicus was completed, the first university botanical garden in the Netherlands.

The question of how many pharmacists actually emigrated to the North after the fall of Antwerp is difficult to answer because the archives give little information on this. It is conceivable, however, that a pharmacist does not readily abandon his pharmacy since the preparation and dispensing of medicines is necessary always and under all conditions. As far as Leyden is concerned, we know that by 1610 half of the 10 Leyden pharmacists were emigrants or descended from emigrants.

One family which had left the Southern Netherlands for religious reasons and settled in the German Hanau near Frankfurt, was that of the merchant Deleboe. Later, in 1658, his son Franciscus was appointed professor of medicine at Leyden (23).

Franciscus Deleboe, or Sylvius, as this descendant of a Southern Netherlands emigrant called himself, considered chemistry one of the main components of medicine. He was convinced that the functioning of the human body could be explained in terms of the chemical processes which happen within it. The period until 1672, in which Sylvius was active at Leyden, can be regarded as the height of 'iatrochemistry'.

Not only did his library include many medical texts, but also various botanical and alchemistic-chemical works (24). In addition, he also possessed pharmacopoeiae, such as the 'Pharmacopea Augustana'. In 1653, at Gouda, an edition of this book appeared, in which the rise of iatrochemistry is clearly apparent in a separate appendix of more than 100 chemical preparations.

The 'pharmacopoea spagyrica' by Johann Glauber also belonged to the library of Sylvius, who in his home on Leyden's Rapenburg had two rooms equipped as laboratories to carry out his own chemical-pharmaceutical experiments. There he prepared mixtures, amongst which his volatile salts became especially well-known. These were alkaline products which he prescribed to 'neutralize the acidity in the body'.

But however much Sylvius propagated iatrochemical thinking, it is obvious that the preparations linked with his name are for the mostpart composed of traditional, galenic materials. His 'Diascordium Sylvii', a classic recipe, related to the Theriak, is mentioned in the final edition of the Leyden pharmacopoeia in 1770.

We have to realise, however, that chemistry in the 18the century was still at the beginning of its development. In the different publications of books of prescriptions from North and South Netherlands towns, appearing between 1636 and 1795, the breakthrough of chemistry is evident from the increase in the number of chemical preparations, and by the titles of these pharmacopoeiae in which the supplement 'Galenico-chymicum' gets more prominence. Such a supplement occurs for the first time in a Southern Netherlands pharmacopoeia which appeared in Antwerp in 1661.

Only under French rule did the publication of town pharmacopoeiae finally come to an end in both the Southern and Northern Netherlands.

During the regime of the Batavian Republic, the Northern Netherlands witnessed the introduction of a national book of prescriptions, the 'Pharmacopoea Batava' which appeared in 1805. The publication of a national pharmacopoeia was never realized in the Southern Netherlands, despite the plea of the Brussels pharmacist Van Mons, who in 1800 even spoke of a European pharmacopoeia (25).

In November 1813, the Northern and Southern Netherlands united in the 'Kingdom of the Netherlands'. Pharmacists fervently hoped for the long-awaited reform of their training. To their great dismay, however, no mention was made of a university education in the medicine Act of 12th March 1818. This act even gave country physicians permission to dispense medicines, which pharmacists considered a violation of their long-standing monopoly in the sale of medicines. The pharmacists were not even consulted in the compilation of the new book of prescriptions, the 'Pharmacopoea Belgica', which was published in 1823. We can assume therefore that they were not too well-disposed towards King William I.

In 1822 the University of Ghent, established by William I in 1817, appointed a Dutchman as Professor of botany, zoology and comparative anatomy, namely Jacobus Gijsbertus Samuel van Breda (26). He was also in charge of the Hortus Botanicus and under his management the Museum of Natural History was radically expanded. Van Breda was a highly dedicated teacher and an important natural scientist. The national upheaval of 1830 put an abrupt end to his Ghent career and he returned to the Netherlands.

After the separation of the Netherlands and Belgium, a university education for pharmacists finally became reality : in Belgium as early as 1849, and in the Netherlands after 1865. Both countries went their separate ways, and this also applied to the area of pharmacy. Nevertheless, the pharmaceutical heritage left behind by great scientists and preserved in the excellent work of the printers, has in part fallen to us.

In this historical review, most attention has been given to the 16th and 17th centuries, the age of Humanism and the Renaissance, in which scholars and scientists diligently contributed to our inheritance and thus laid the foundations for our common pharmaceutical past. Particularly the Southern Netherlands contributed in large measure to this.

In the near future, after 1992, we will see again the pursuit of harmonization in the field of pharmacy (28).

As early as 1969 the first part of the European Pharmacopoeia was presented to the secretary-general of the European Council. In 1987 mutual recognition of our pharmacists' diplomas was achieved. Training will also aim at meeting common standards, and a European registration system is to result in the uniformity of medicines.

The Belgian and Dutch Societies for Phytotherapy are already part of the European umbrella organization, the ESCOP (29). And thus our paths converge again. It seems advisable therefore to remain aware of our common heritage as we proceed together.

For the last 40 years the 'Kring voor de Geschiedenis van de Pharmacie in Benelux' (Society for the History of Pharmacy in Benelux) has been studying the pharamceutical past, in which the pharmacist, the preparer of medicines from way back, occupies an important place.

This historical study supplies some unexpected views of the past and the future.

Sarton also pointed this out to us in his 'new humanism' (30). In his own words : "The present without its past is insipid and meaningless; the past without the present is obscure. The life of science, like the life of art, is eternal".

His new humanism did not result in narrow specialism, but in what he refers to as a 'double Renaissance', which also incorporates nature, culture and man.

In this way an inspiring influence emanates from the past and thus our common pharmaceutical heritage can form a link between our nations.

In turn this can contribute to the process of evolution which is necessary to realize harmonization within the framework of the European Community.

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LAUDATIO

Prof. Dr. J. Hoorens

Prof. emerit. Rudolf Fankhauser was born in Switzerland, in the Canton of Bern. He became doctor in veterinary medicine in 1945 at the University of Bern. He spent shorter or longer periods of post-graduate education in many places of his home country and abroad, f.i. from January 1948 to spring 1949 in Alfort/Paris and afterwards some months at the Veterinary School of Vienna.

On from 1945, he was a research fellow of prof. Dr. med. E. Frauchiger at the Department of comparative Neuropathology in Bern. In 1952 he worked at the well known Bunge Institute of Prof. Dr. Ludo van Bogaert in Antwerp. Between 1962 and 1968, he was in the U.S.A. for 4 periods of several months each, mainly at the University of Pennsylvania, Philadelphia and at the Armed Forces Institute of Pathology, Washington DC.

After his promotion to private-docent for comparative neuropathology in 1951, he became Professor extraordinarius in 1955 and ordinarius in 1966. Besides his occupation with comparative neurology, he was also active in the Ambulatory Clinic during many years. He was Dean of his Faculty and was Rector of the Berne University during the period 1980-81.

His performance made that he became Doctor honoris causa of the Universities of Torino, Hannover, Ghent and Philadelphia (Univ. of Pennsylvania).

Prof. Fankhauser was also interessed in the history of veterinary medicine and published a number of papers mostly on the history of Swiss veterinary medicine. Therefore it was an excellent oportunity to propose our doctor honoris causa as a candidate for the Sarton-medal.

The Sarton committee agreed with the proposition and invited him for giving his lecture on "The development of veterinary medicine in Switserland during the 19th century".

THE DEVELOPMENT OF VETERINARY MEDICINE IN SWITZERLAND DURING THE 19TH CENTURY

R. Fankhauser

The title of my talk indicates its essential content. I was asked, however, to imbed it to some extent into the history of our art in general. I shall try to do this, but with two important restrictions : first, I am not a professional historian. I just share with them the fate of talking about a period of which I have no personal experience! Second : we are limited in time.

My general remarks will therefore be rather arbitrary. You all know that man, on from the first domestication of animals — going back some 10'000 or more years — tried to prevent and cure their ailments, as he did for himself (1).

Wherever civilization concentrated, in Egypt, Mesopotamia, China, the Anatolian, Greek and Roman, the Arab world, animal medicine developed, most times together with human medicine. The convulsions of mans history— rise and fall of the empires — let the art flourish or disappear. What was left of the ancient world was taken over by the Arabs, amalgamated with Asian wisdom, developed in centres like Andalusia and from there handed over to the European Middle Age through scientists, of whom many were Jewish. Knowledge was — selectively — preserved, but usually not furthered, in many medical schools like Salerno, Bologna, Padova, Montpellier, Paris, Oxford, to mention only a few. Medicine was essentially conservative, basing on the knowledge and works of ancient authors, especially Galenus. University medicine was preceeded by the so-called monastic medicine, which should not be over-estimated. In the 9th century, the famous library of the monastery in Saint Gall had only six medical books, in contrast to about 1000 on theological matters! (2)

Treatment of animals was essentially in the hands of farriers, herdsmen, hunters, falconers, at the best of equerries and other more or less educated people. If somebody — I only quote *Carlo Ruinis*' "Dell' anatomia, et dell' infirmità del cavallo", Bologna 1598 — marked an outstanding progress, his heritage was soon brought down to popular levels by numbers of imitators.

Critical mind and willingness to observe nature instead of compiling and exploiting so-called classical writings began to dominate in the Renaissance and the following centuries. They brought a wealth of information about animal anatomy and diseases, to a large extent by the work of physicians. Just one example : *Johann Jakob Wepfer* (1620-1695) founded a small, but famous medical school in Schaffhausen on the Rhine. *Harder* who described the lacrimal gland of deer and *Peyer* with this "Merycologia sive de ruminantibus et ruminatione commentarius" — the precursor of ruminant physiology — were two of his prominent scholars. *Wepfer* himself studied Coenurosis in cattle as a model of human vertigo, using, therefore, the comparative method (3).

Applied veterinary medicine, however, did hardly take advantage of this flow of knowledge, and went on as it had done for centuries. Crude and uncontrolled treatments were common, and the authorities ordered partly useless and stupid measures against epizootics. Maybe the best ones protected humans against rabid dogs — or tried doing so. In 1810, there was an outbreak of canine rabies in our town. the order was to kill all of the about 9000 cats. It was a tremendous problem for our mild-hearted Ladies hiding their belowed pets — nearly as important as the marriage of Napoleon with Marie Louise!

Mrs. *von den Driesch* is certainly correct when she says that the "cure" was often more noxious and certainly more painful than the disease itself (4).

I am old enough to know that, what I had learned and applied to the best of my knowledge, is now considered to be in part between useless and disastrous! Man's convictions are a strange thing; but can you exist without them ?

The veterinary profession — if we wish to use this term — was lacking of cohesion, of a common philosophy, being split into parts according to its objects. Even the most advanced — horse medicine — was in the hands of farriers and horsemen. But the demand of the armies, with millions of horses, finally enforced the foundation of Veterinary Schools and the formation of more solidly trained people. In addition, numerous and extremely devastating epizootics had sometimes as much influence on the outcome of wars as had the military actions themselves. Empress *Maria Theresia*, in the founding act of her Vienna school, urged not to neglect "the civilian sector". Which, by the way, did not prevent this famous institution from becoming a nearly exclusive horse establishment for over hundred years!

Human doctors, whose insight was in no way beyond doubt, were officially the supervisors of epizootic diseases. Exept for quarantines, nothing reasonable was done. And quarantines were rather due to politicians — often identical with cattle traders — than to physicians. In the flourishing trade accross the Alps between Italy and Switzerland, they had functioned for centuries — without the Common Market!

Human medicine — to be honest — was largely ineffective. The great plagues had disappeared from Europe, merely by slight improvements of hygiene and changes in human behaviour — and thanks to the Genius epidemicus! The helplessness of medicine in front of tuberculosis and syphilis, f.i., was typical. Academic medicine was entangled in theories. The most efficient branch, surgery, had long been left to barbers and other non-academic people. Sometimes, one of those "quacks", due to his intelligence and his psychological intuition, became famous. So was *Michel Schüppach* of my home country, who treated distinguished patients from Antwerp to St. Petersbourg.

Finally, in the second half of the 18th century, time was ripe for a better education of veterinarians, for the foundation of veterinary schools. The first two, as you all know, were Lyons and Alfort in France. Founded in the sixties of the 18th century by *Claude Bourgelat* (5).

Bourgelat, horseman and politician, friend of influential people, is a symbol for the fact that new ideas do not necessarily originate from traditional sources. His competence was rightly questioned by *Lafosse* père et fils — his merit remains untouched!

Up to the end of that same century, about 30 schools were founded in Europe, most of them by monarchic decree and most often run by people — physicians and others — who had been sent to France.

The development during more than hundred years was not at all easy, the resistance of "popular medicine" being strong. According to van den Driesch (6), in the Free State of Bavaria, 926 certificated veterinarians still competed with 310 registered animal healers — in 1925!

When tracing now the history of my own Bernese school during its first hundred years, I hope to convey also an impression of the slow, but steady development of our profession.

Towards the end of the 18th century, Berne was still an important but somewhat sleepy State in the centre of Europe, oligarchic, patrician and patriarchal. It was prosperous, austere and parsimonious. Berne was one of the leading Republics of the loose and manyfold Swiss federation. It had reached its political culmination after the Burgundian wars — you may know that its attitude in front of *Charles le Téméraire* was somehow different from that of the City of Ghent!

— but withdrew from the great European politics after te bloody defeat of Marignano in 1515. The flourishing export of mercenaries for over 200 years (16th to 19th centuries) is another matter not to be discussed here. But it was a long period of relative peace — although not for the Grisons, invaded repeatedly by French, Austrain and Spanish armies.

In the Republic of Berne — dominated by the town, but respecting rather scrupulously old rights and privileges of smaller towns and rural areas — a rustical, non-commercial, nearly anti-industrial attitude prevailed. The 17th and 18th centuries were a time of flourishing peasant civilisation.

When the French armies invaded the country in and after 1798 and brought the blessings of the Great Revolution — liberté, égalité, fraternité — the old order faded away. The state had to adapt to the new conditions and — seen from the distance — did extremely well. A plundered, impoverished, exhausted country mobilized its intellectual resources. Between a number of national organizations — still in existence — the Swiss Veterinary Association was founded in 1813. Its leading spirit was a physician, *Franz Karl Stadlin*, of Zug.

A few years before, on the initiative of its chancellor *von Mutach*, the old "Hohe Schule" — the precursor of the University of Berne — had been revitalized. It was founded in the time of the Reformation, and — according to the practically oriented Bernese politics — had to form mainly clergymen, the observers of the people and prolonged arms of the government. It was now called the "Academy".

Speaking of clergymen, a short digression may be permitted : in many parts of Europe, catholic and protestant, an often considerable part of the income of the minister stemmed from the church farm. Knowledge of its management was therefore vital. Educated as they were, the priests played an important rôle in the advancement of the agricultural sciences. My friend *Hörning* has found an article were the activities of clergymen in veterinary medicine — as part of agriculture! — are vividly defended. It was published in the "Magazin der Vieharzneykunst" — probably the oldest veterinary journal in German — in its first and only issue of 1784!

The Bernese Academy of 1805 had 4 faculties : Theology, Law, Medicine and Philosophy. As an appendix to the medical Faculty, it was decided to install a Veterinary School, in order to cultivate "this vital science". The main wealth of the new Canton of Berne - part of the République helvétique une et indivisible and living under the constitution mediated by Napoleon Bonaparte — stemmed from agriculture.

The next step was to find a teacher for the newly established school. The local candidates were all found to be insufficient, and finally Prof. *Emmert* — henceford called "the elder" — anatomist and physiologist of the medical Faculty, suggested to try it with his younger brother *Carl Friedrich*. He was a graduate of the Tübingen medical Faculty and had heard lectures on veterinary matters given by Prof. *Ploucquet*. He was elected in spring 1806 and started lecturing in November, with one student! Three years later, the first 3 students (the total number having increased to 11 within 18 months) graduated. In 1812, *Emmert younger* was made Professor of surgery and obstetrics at the medical Faculty and began to neglect — for financial reasons between others — his activities in the veterinary School. Some years before, the young institution had found its first accomodation in old buildings of the Burgerspital (Hospital for old citizens). The Burgerspital — a beautiful classicistic building —contrasts today strangely with the modern construction of the Railway Station next to it! On from the beginning, there was much dispute between the school and its surroundings, especially concerning post-mortems performed close to habitations. Finally, they had to be done in an old tower of the medieval walls, down at the riverside!

The school entered a critical period when *Emmert* was appointed by the medical Faculty. The Academy decided to have a pair of young, local people trained and offered two grants for a 3-years period to be spent in foreign Veterinary Schools.

Matthias Anker (1788-1863), who had successfully graduated in 1811, competed and won, together with *Peter Schilt* (1787-1845). In the autumn 1812, they left Berne. *Anker* went to Vienna (*Schilt* to Berlin), from Ulm on the Danube, an 11 days boat journey (with extremely poor food, as he wrote back home!). *Anker* studied in Vienna for nearly 2 years, with one interruption for a study trip (per pedes!) in Hungary, were he visited studs, cattle- and sheep farms. In the fall 1814 he walks from Vienna to Berlin, where he stays until the end of March 1815. His intention to visit *Viborg* in Copenhagen and to end his trip in Alfort is prevented by the political situation. Astonishingly enough, the historical turmoil in Europe had otherwise rather little influence on his plans! He finally reaches Munich, visiting many places and interesting persons in between.

Back in Bern towards the end of 1815, the two candidates were thoroughly examined by a committee of the medical Faculty early in 1816, then appointed as veterinary teachers — provisionally — with a yearly salary of 800 pounds Bernese! *Emmert* remained Director of the school and teacher of anatomy and physiology. When *Schilt* returned to his native Oberland — as practitioner of human and veterinary medicine! — in 1819, *Emmert* wanted to teach surgery again, but the students preferred *Anker*. The conflict was perfect. *F.A. Gerber*, a young physician, was elected prosector and probably did most of the anatomical and physiological teaching. He was one of the earliest pioneers of photography, but his claim for priority against *Daguerre* seems unwarranted.

In 1826 finally, the school could move into new quarters, were it remained for nearly 140 years. It was a property next to the old rifles ground, 5 minutes out of the city walls, with a building originally concieved as a brewery. Years later, it is described as a lovely meadow with running fountains and with fruit-trees, high above the river, in an agricultural environment; seemingly an idyllic place. But bad enough, the knackers yard and the cemetery of the prison were its closest neighbours! Under *Anker*'s rule, stables and a smithy (which shoed about 2000 horses a year) were built.

The political shift after 1832, called the Regeneration, brought democratic forces to power. It was soon followed by the transformation of the old Academy into an University, in 1834. The Veterinary School was again incorporated in the medical Faculty, as a so-called subsidiary institution. The same year, *Emmert* died in Interlaken. *Anker* was officially made principal of the school. The teaching staff was enlarged by *H. Koller* and *J.J. Rychner*.

The first of them was a very quiet figure, mainly teaching botany, pharmacology and materia medica. He was also in charge of the library, which — as it seems — did nothing than decay in his hands. In a satyric newspaper of the forties, it was said that he was distinguished only by his capital moustache; and in fact, the late biographer has nothing to add! *Rychner*, on the other hand, was an interesting, over-active, partly brilliant but controversial person. Born in Aarau in 1803, he had studied in several veterinary schools including Berne (7). He worked first in his native town as meat inspector and then went to Neuchâtel — a Prussian principality! — as government veterinarian. Here he failed practically. This was partly due to his physical appearance : he was a tiny man, as you would expect from his youth-portrait; a late one simulates a rather sturdy fellow. The political wind blew him to Berne. In some way or another, he managed to join the teaching staff of the Veterinary School. In 1839 he was already professor; no doubt, he was carried upwards by the radical wave.

At this point, one more digression : in 1835, *Samuel Anker* (1790-1860), brother of *Matthias*, takes the position in Neuchâtel abandoned by *Rychner*. He studied in Berne after his brother, made the diploma in 1814 and practised in his native village Ins (Anet) for 20 years. Their father — his certificate still exists — and grand-father had been country-veterinarians, farming and cattle- and horse-trading as a supplement to their scarse income. Father Anker *built* a big farm-house in Anet, which today is a site of pilgrimage. But not because it was the home of veterinarians. *Samuels* only surviving son *Albert* became a painter (instead of a vicar as his father had foreseen) : conservative, traditional, but very popular and today again en vogue. *Samuel* died — of cancer — in his brothers home in Berne. The only existing portrait is a drawing, made by his son, of the dead father. It still hangs in the Anker-house in Anet. *Rychner* — whom *Matthias Anker* profoundly disliked — was probably withheld by him from an extensive horse practice. So he directed his energies towards cattle. In 1835 already appeared his volume on the diseases of cattle, or Buiatrics. At that time, he must have had a minimum of personal experience — by far inferior of that of the two *Anker's*. But the book had 3 editions and secured him — at least in the reach of the German language — the fame of a founder of buiatrics.

Rychner wrote a lot : several books and a great number of monographs and articles in veterinary and agricultural journals. His critics said that he was writing much, but thinking much less! And they are not thorougly wrong. He, however, did another thing to perpetuate his name : he founded an Ambulatory Clinic — on his own expense, as he stressed — which was developed further under so capable successors as *von Niederhäusern, Hess, Wyssmann* and *Hofmann.*

The 28 years within the Academy (1806-1834) may be considered as the initial period of the Veterinary School, or the period of development. It was dominated by the personalities of *Emmert* and *Anker*. The following period was one of stabilization and than decline. It is identical with the 35 years as a subsidiary institution of the new University. During its early 20 years — politically a much troubled time for the Canton — the school was quite active. *Anker* was fighting for a better position of the veterinarians, for improvements of meat inspection and control of knackery, of horse- and cattle-breeding, for better regulations concerning epizootic diseases, and he published his standard books on diseases of hoofs and claws. The activities of

Rychner were already mentioned. *Gerber* the anatomist, as well, did good work. Between other things, he published a beautiful atlas on horse anatomy in common with the painter *Volmar*. Only *Koller* persisted in silence! After the midfifties, however, the fire burnt down. *Anker*, already sick over years, died in 1863. The remaining 3 were sent to pension in 1869. A government decree of 1868 — although saying that the School was an institution "linked with the University" — marked in fact the expulsion from it. An active fraction of the medical Faculty was behind this decision and —regarding the facts calmly — one must say that it was well founded. It is now the moment to look at other parts of the country, because Berne is not Switzerland!

Amusing inset : in 1846 — just before our last Civil War — the Canton of Valais founded its own, bilingual, veterinary school. But after its first course, it disappeared again.

In 1820, the school in Zurich was founded. It had very difficult periods over years and was often close to suppression. During all the 19th century, it was never attached directly to the University. One of its outstanding teachers of the early period was *David Wirth*, physician and veterinarian. He was also for a time editor of the Swiss Veterinary Archives and in this period secured order and regular publication. (The journal has been founded in 1816 — and still exists). *Wirth* died in 1849, with 56 years, and his successor was *Rudolf Zangger*, with only 23! He was elected so-called second main-teacher. Only in 1834 had the school been consolidated by a law; its revision in 1848 provided better financial support, increased the duration of the studies from 2 to 3 years, and promoted the first main-teacher, Professor *J.J. Hirzel*, to director of the school. *Hirzel* died already in 1855, only 49 years old (and leaving behind a son who later on fought in the North American Civil War). *Zangger*, 29, was elected first main-teacher and Director of the school. He was of very modest provenience, but gifted with sharp intelligence, limitless working capacity and probably equal ambitions. He immediately had a heavy load of teaching obligations, contrasting with the paucity of his salary. After the death of *Anker*, he negotiated with the Bernese government about the directorship of that school. When the Zurich government offered him the same salary, he found Zurich more attractive. This even more so because nobody supported his plans for *one* federal school. *Zangger* had been editor of the Schweizer Archiv für Tierheilkunde from 1849 to 1855, together with *Rychner*, but probably carrying most of the load. He was it again — this time alone — from 1855 to his death in 1882. He was president of the Swiss veterinary Association from 1853 to 1856 and -reelected in 1861 — held the function again until he died. Both went asleep under his hands. This is not a reproach : because *Zangger* was active and often successful, he was overloaded with problems — which the others hoped he would solve! And it seems that he could hardly say "NO"! He organized the 50-years celebration of the Swiss Veterinary Association in 1862 and the 3rd International Veterinary Congress in Zurich 1867. He was federal Commissioner for the (successful) fight against Rinderpest 1870/71 and as such precursor of the later Director of the Federal veterinary Office. Having served during the short civil war in 1847, he advanced rapidly as a veterinary officer and reached the rank of a colonel. His influence for better positions of the veterinarians in the army was remarkable. During the Franco-Prussian war, he was acting as Chief-Veterinarian of the army, but later on refused to accept this position as a full-time job.

But *Zangger* was also an active politician. Member of the democratic party, he was in the cantonal parliament with 32 years, later in the National and in the States Council (Ständerat). He was a leader in the campaign for democratic revision of the Zurich constitution. *Zangger* was a model for the manyfold political activities — from community to federal levels — of veterinarians. It is a pity that this has largely disappeared; not to the advantage of the profession!

The countless activities of *Zangger's* withheld him more and more from his primary task : Director and teacher at the Veterinary School. During the seventies, there was a constant flow of young coworkers away from Zurich. The last important action of *Zangger* was probably that he attracted a gifted young man and won him for the school : *Erwin Zschokke*, who soon became the leading figure of the school — later on : the faculty.

Now back to Berne : the last 30 years of the century may be named the period of hopes, deceptions and devotion. In 1869, as we have seen, the government had made tabula rasa. A new director was elected, professor *Pütz*, 40 years old, ph. D. of the University of Rostock, graduated as veterinarian in Berlin 1850. He was an energetic and active man; and on from his first days in Berne was fighting for improvements of veterinary education and for the re-integration of the veterinary School into the University. Some other teachers from Germany were elected with him. When they slowly moved back to their home country, they were predominantly replaced by Swiss people. Quite a few of them came from Zurich. In general, it was a young staff : I'm counting 8 who were between 24 and 31 in the seventies and eighties.

Despite some adversion from certain sides, co-operation with the medical Faculty was intensified : *Guillebeau*, pathologist, acquired the MD and medical diploma during his first years in Berne and the anatomist *Rubeli* made his MD-degree as well. *Marcelli Nencki, Balthasar Luchsinger, Hugo Kronecker*, all of the medical Faculty, instructed biochemistry and physiology to veterinary students. General matters like physics, chemistry, botany were offered by the philosophical Faculty. During te same decennies more and more matters shifted from cantonal to federal competence.

It's not my ambition to bore you with data : control of foodstuffs with the so important branch of meat inspection, regulations of trade of animals and materials of animal origin, control of epizootics and other economically important animal diseases, regulations of training programs and exams for the medical professions and — depending from it — the right of exerting ones profession in all Cantons, reorganization of the army including the veterinary services, may all serve as examples.

No wonder that the two Veterinary Schools did not escape to such trends of unification. An inquiry committee proposes, in 1884, the establishment of a Federal Veterinary School, and the teachers of Berne and Zurich support this proposal, considering the rather poor state of their institutions. In 1889 and 1890, the Federal Assembly declares the plan "important" (erheblich). But none of the two cantons is ready to abandon its school, and the Confederation has plenty of other problems. Once more, parochialism (the Swiss term is "Kantönligeist") was stronger.

Historical reminiscence : seventy years before, the physicus of the town and canton of Basle had already proposed the establishment of a Swiss Veterinary School!

Anyway, the ferment worked : the Bernese Grand Council decided to build a new Veterinary and Farriery School, to the price of about half a million francs. In 1891, a fire destroyed part of the old main building, including a large number of books in the library. In 1895, the new buildings — in the same area — were ready and could be proudly demonstrated to the VIth International Veterinary Congress held in Bern. Its successful secretaries were professors *Berdez* and *Noyer*, both perfectly bilingual.

(In parenthesis : *Louis Pasteur* was made honorary member of the Congress. He thanked with a telegram saying that the veterinarians were the first to recognize the importance of his new doctrines. Ten days later, he died!)

I called the last third of the century one of devotion. Both in Berne and in Zurich, the few Professors, with a heavy load of teaching and more than modest facilities, did research work in bacteriology and pathological anatomy, were involved in animal husbandry, in the struggle against epizootic and other economically important diseases, in meat and milk control and — last but not least —in the hardships of public instruction. And some of them had not the starting conditions considered normal today. *David von Niederhäusern*, f.i. — he became

Director of the School with 30 years, after *Pütz'* departure for Halle-had only frequented country schools and then an agricultural college, where he felt at first far behind the other scholars. He died at the age of 34; tuberculosis and restless work killed him.

Ernst Hess, who was made a teacher with 24 years, a farmers son, had left the classical grammar-school after two classes — at that time still customary. He became one of the most famous buiatricians. After the re-incorporation of the school into the University, he had to work out a doctoral thesis, in order to maintain his position as a professor! At that time, he had passed the forties. He died in 1920, of coronary sclerosis.

This epoque of hardship, with a study program nowadays considered absolutely insufficient, produced valuable men. I only mention *Sir Arnold Theiler* of Onderstepoort, South Africa. He published a paper on Horse-malaria in 1901, which he submitted to the Berne Faculty as his doctoral thesis (8). His temporary co-worker *K.F. Meyer*, lifelong Director of the Hooper-Foundation in San Francisco, already belongs to the 20est century.

During the last decade of the 19st century, the Swiss Veterinary Association and the two Veterinary Schools pushed in the same direction. At the annual assembly of the Association in 1898, it was unanimously stipulated that the "maturity"-certificate, i.e. full grammar-school education, should alone give access to the Veterinary Schools. *Conrad Eggmann*, distinguished practitioner and local politician, and Prof. *Rubeli* of Berne were the rapporteurs. Both were later made honorary Doctors of their Faculties, and honorary members of the Association — highly deserved distinctions.

Early in 1899, the teaching staff of the Berne School proposed to the government the re-integration into the University. On the 11th of December, a federal decision postulated equality of conditions for all medical students, human and veterinary. With this, the way was free, and in a public vote of January 21st 1900, the Bernese people accepted, with huge majority, the "Law concerning the integration of the Veterinary School into the University".

The Bernese Minister of Public Instruction, *Albert Gobat*, Jurassien, had been an important positive factor. By the way : in 1902, he won the Peace-Nobel-Price for his efforts concerning the reconciliation of France and Germany after the war of 1870. He had the privilege to die on march 16th, 1914.

The Canton of Zurich soon followed the Berne example. After World War II, the problems of housing — again acute — were solved for both Faculties.

Ladies and Gentleman : the title of my presentation is not just a title, but also an obligation. Whith the last sentences, I already penetrated into the 20est century — our century which will soon enter its last decade. May it end as did the 19st : in relative peace and full of hopes. And may the hopes be better realized.

To conclude : for the future of our work at least, i have good reasons to be optimistic. My successor is a former student of the University of Ghent. He has been sent to us by one of the most outstanding neurologists of our time, *Dr. Ludo van Bogaert*, who died a year ago in Antwerp.

For this heritage, and for the honour of the *Sarton* medal and lecture — and certainly also for your patience — I am very grateful.

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Notes

(1) Mammerickx M.: Génèse de la pratique, de la recherche et de l'enseignement vétérinaires dans le pays flamand. Sartoniana *1*, p. 115-134 (1988).

(2) Ackerknecht E.H. : Geschichte der Medizin, 3. Aufl., Stuttgart (F. Enke) 1977.

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(5) Mammerickx M. : Claude Bourgelat, avocat des vétérinaires. Bruxelles, chez l'auteur, 1971.

(6) see footnote 4.

(7) The Swiss, despite the existence of two veterinary schools since 1820, had to pass examinations in their individual cantons. Some French speaking people studied in Lyons or Alfort, Alemanics in Karlsruhe and Stuttgart, and a few from the Italian speaking valleys sometimes went to Milan. This was still possible up to the end of the century, although there were federal regulations on from 1880. See also footnote 1.

(8) Theiler A. : Die Pferde-Malaria. Schweiz. Arch. Tierheilk. *43*, 253-280 (1901) and Inaug. Diss. vet. med. Univers. Bern 1901.

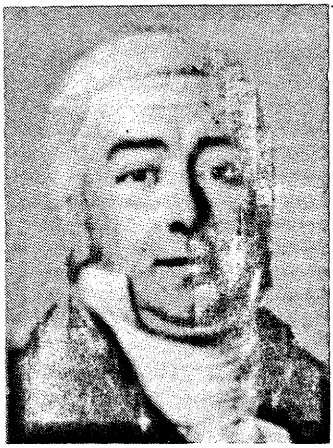

Fig. 1 : Chancellor Abraham Friedrich *von Mutach* (1765-1831), founder of the Bernese Academy.

Fig. 2 : Prof. Carl Friedrich *Emmert*, 1780-1834, first teacher and Principal of the Berne Veterinary School.

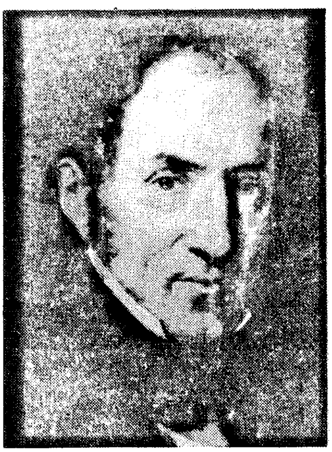

Fig. 3 : Matthias *Anker*, 1788-1863, Professor and 2nd Principal of the Berne Veterinary School.

Fig. 4 : Prof. H.J. Theodor *Pütz*, 1829-1898, Director of the Berne Veterinary School from 1869 to 1877.

Fig. 5 : Prof. David *von Niederhäusern*, 1847-1882, Director of the Berne Veterinary School from 1877 to 1882.

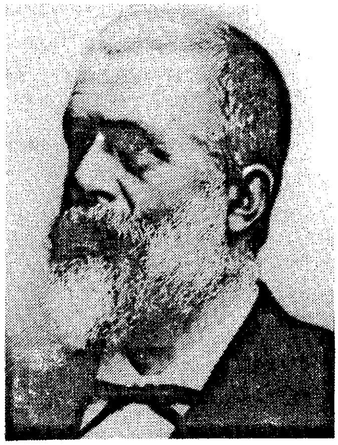

Fig. 6 : Prof. Henri *Berdez*, 1841-1901, Director of the Berne Veterinary School from 1882 to 1900.

Fig. 7 : Albert *Gobat*, 1843-1914, Director of the Department of Public Instruction, Canton of Berne, from 1882 to 1906.