THREE DECADES OF ANTIHYPERTENSIVE THERAPY

A historical representation of the main events of a truly revolutionary period of drug research which led to a rational medical approach in the treatment of hypertension is to shed light on the conversion of pharmacological substances into therapeutic concepts.

In 1830 Lobstein spoke of vessel changes as one of the main causes of hypertension and the development of CHD.

It was a long way from explanation and description of the blood-circulation by William Harvey in 1628 to the establishment of essential hypertension as a clinical picture itself around the turn of the century.

Now I would like to present in short some treatment concepts. Thiocyanate therapy as a concept of innovation in 1903 was a first symptomatic treatment approach. After having been propagated by Marlon Herbert Barker in 1936 and described in 1945 by Page and Corcoran in their classical manual of hypertension, it was then recommended in combination with vitamin A and surgical intervention (exeresis of splanchnic nerves) as treatment regime.

In World War II Hans Herrmann Bennhold tried thiocyanate therapy against hypertension.

I may now come to the mercurial diuretics which had been used since their discovery in 1924 for regulation of the renal water/salt balance. However, it was not before 1948 that their antihypertensive effect was shown by Megibow at the New York Mt. Sinai hospital. Due to their toxicity, worldwide clinical use was prevented.

The discovery of the diuretic effect of azetazolamide in 1950 initiated the development of the non-mercury containing diuretics which were less toxic. Although at the beginning they were not intended for antihypertensive therapy Hollander and Freis observed in 1957 a moderate, longer sustained blood pressure reduction in patients treated with chlorothiazide. The introduction of thiazides in 1958 was an advance.

The chemical structure of the chlorothiazide offered unlimited possibilities of modification for new substances with a greater potency, longer RR-reduction and less potassium loss. Especially chlorthalidone and clopramide fulfilled these requirements as diuretics in 1959. In 1962 MSD (Merck, Sharp and Dohme) developed ethacrynic acid which was introduced in 1965 as a highly effective diuretic for oral and intravenous administration.

The search for a sodium-selective effect on the electrolyte excretion led to spironolactone which inhibited the effect of aldosterone in the renal tubuli. This
was to reduce potassium excretion which was demonstrated first by Wiebelhaus in 1965.

In 1968 triamteren was found to have a sodium-diuretic and potassium-sparing potential which was ideally suited for use in diuretic combinations.

The potassium-sparing diuretic amiloride, which had already been described in literature by Bull and Laragh in 1968, was introduced in 1970 and was also used in combinations.

A further thiazide derivative via a molecular modification of benzothiadizine is diazoxide introduced in 1970 which has an antihypertensive and vasodilator effect via a decrease in peripheral vascular resistance and an increase in cardiac output. It is used as « Hypertonium » in emergency situations.

I may now briefly come to methyldopa, in October 1958 a NIH symposium chaired by Udenfried was held in Bethesda, Maryland (USA) which dealt with alpha-methyldopa and its pharmacological as well as toxicological properties.

In 1959, following his observations at the NIH in autumn, L. Sjoerdsma had to persuade the pharmaceutical company Merck, Sharp and Dohme to develop by 1962 methyldopa as an antihypertensive agent in own laboratories. In 1963 Bayer (Leverkusen) came onto the German market with Presinol, and also in 1963 Boehringer-Mannheim introduced Sembrina onto the market.

One year later it was launched in the US as Aldomet. It can be said that here a biodynamic hypothesis had stimulated drug research and the pharmaceutical industry to introduce potent substances onto the market.

I may proceed to clonidine. Clonidine preparations which were developed in the laboratories of Boehringer company (Ingelheim) have been available on the market since 1966. In 1975 the FDA (USA) approved this imidazoline derivative which had been modified by Höfke and Kobinger in 1966, as antihypertensive therapy in the US.

I would like to summarise previous steps taken for a more precise diagnosis and medical treatment.

On 18 April 1944 the first institute of cardiology was founded in Mexico City with essential participation of Ignacio Chavez.

It was not before 1951 that Sir John McMichael (Professor of Medicine) founded the first hypertension clinic at the Hammersmith Hospital in London. Sir Horace Smirk who left London and went to the Otago Medical School in New Zealand tried to convince the still sceptical medical profession by his positive experience made with an antihypertensive hexamethonium therapy which was carried out at the Dunedin Hypertension Clinic in New Zealand.

The ganglion-blocking agent hexamethonium opened the gateway to a differentiated pharmacotherapy. It was the first effective drug in malign hypertension and was introduced in 1950 into practice. The therapeutic value of ganglion-blocking agents was postulated in 1946 by Acheson and Moe. Via his search for a competitive antagonist of dexamethonium Sir William Paton came to the pharmacological effect of ammonium salts. The ganglion-blocking agents as « chemical sympathectomy » were a logical consequence in 1947, since hypertension was seen as a symptom for a disturbance of the autonomic nervous system.

Hundreds of ammonium salts were synthesised afterwards and especially the diquaternary ammonium compounds became the centre of interest. In 1949 the dosage of hexamethonium-iodide used in the clinics was 0.24 mg/kg bodyweight.

In practice, these first chemical substances for treating hypertension showed an interaction of pharmaceutical and therapeutic effectiveness.
In 1956 bretylium was developed in research programmes of the Wellcome Laboratories in England as precursor of the adrenergic neuron blocker guanethidine which blocks the transmission of sympathetic impulses in the post-ganglionic region. Its antihypertensive effect was described in 1959 by Page and Dustan.

It was introduced in Germany in 1960 by Ciba under the trade name Ismelin.

On this slide you see Heinz Losse being the first scientist and clinician who reported on the effectiveness and mode of action of alkaloids from Rauwolfia-serpentina in arterial hypertension. By 1952 different Rauwolfia alkaloids had been isolated. In 1953 the first pure Rauwolfia preparations were introduced in Germany as antihypertensive agents, followed by reserpine combination products as of 1954.

I would like to give a clinical of reserpines: Clinical trials conducted by Arnold and Bock and in the English-speaking areas by Wilkins/Judson and Cronheim in 1952 to 1954 confirmed the blood-pressure lowering effect of Rauwolfia products. Due to the sudden big need for Rauwolfia roots the Indian government, in 1953, had to place an export ban on this root which led to new research activities so that by 1954 20 different Rauwolfia alkaloids were found which were used in hypertension.

In January 1954 Damm and Trautner published their own experience made with the Rauwolfia-alkaloid reserpine in a dosage of 0.5 mg. In 20 out of 44 hypertensive patients the RR-blood pressure was lowered. The combination of Serpasil which he used at that time with the substance 1,4 dihydradrazino-phtalazin (known as nepresol), the blood-pressure lowering effect of which was described by Kühn among others in his publications of 1953, resulted in a blood pressure reduction in patients refractory to therapy. The regime of combination therapy had thus been used with foresight already at that time.

Since 1945 Druey had tested hydrazine-substituted heterocyclic compounds systematically with a view to develop new antiparasitic substances.

Subsequent pharmacological tests by Franz Gross (today in Heidelberg, and previously at Ciba Geigy) showed an antihypertensive effect of 1-hydradrazino-phtalazine in animals. This was clinically confirmed by Reubi in 1950 and Page in 1951.

In 1953 hydralazine was introduced in the US and Europe as an oral, vasodilator antihypertensive. Ciba launched Nepresol, a dihydrallazine, onto the German market in 1955.

During the last ten years the principle of cardiac sympathicolysis has established itself in the treatment of cardiovascular diseases. The discovery of beta-blockers which have practically become the drug of choice in hypertension represents one of the main progresses made in drug treatment during the last 30 years. The development of these substances which cause a competitive and selective blockade of beta-adrenergic receptors enables today a differentiated therapy.

Since the almost speculative research at the beginning of the 1960s a variety of beta blockers has been developed as first generation beta-adrenergic substances.

They were further developed in the laboratories of the pharmaceutical industry and many of them were clinically tested. The almost exponential growth of beta-blocker literature illustrates a fast-growing interest and contributed, as well as the organisation of many specific symposia, to a wide spread of knowledge on a new therapeutic concept.

The question as to what is a betablockade was answered by Barret and Fitzgerald in 1968 as follows: a specific, competitive and thus reversible inhibition of the effects of an adrenergic stimulation classified as typical beta-adrenergic
effects. Subsequently the beta-adrenergic effects of the agonist (catecholamines) are inhibited which has a high affinity for the receptor and a stimulating effect.

The alpha- and beta-adrenergic receptor concept was a by-product of a research programme with a view to find a substance which would relax the vasopressin-induced contraction of the myometrium. Five different catecholamines (arterenole, epinephrine, oxynorephedrine, oxyphedrine and isoproterenol) were tested in vitro and in vivo at the myometrium and ileum.

On the basis of specific differences, mainly in cardiovascular effects, and a specific blockade by specific inhibitory substances a modern concept of adrenergic alpha and beta-receptors developed in the pharmacological laboratory of Raymond Ahlquist at the Medical College of Georgia in Augusta (USA).

It corresponded to the deduced conception of this experimental research to allot to such defined action patterns hypothetical sites of actions at the biological structure, the so-called receptors and to regard stimulating as well as blocking pharmacodynamic effects as interference phenomena at the receptor.

Ahlquist's theory of alpha- and beta-adrenergic receptors was to lead to the development of a new class of drugs. In the last 30 years of pharmacology the heuristic principle of the receptor theory as well as the question of the structure/activity-relationship made clear the mode of action of drugs in the sympathetic — neural and sympathetic — adrenal regulation of the vegetative nervous system.

However, before 1957 not much attention was paid to the classification of adrenergic receptors. In 1958 Moran and Perkins suggested to adopt the Ahlquist terminology and to speak of adrenergic blocking agents.

Ahlquist himself had considerable difficulties in introducing his epoch-making theory into the literature. Nearly 10 years elapsed before his hypothetical ideas were confirmed in experiments.

When defining in 1948 alpha- and beta-adrenergic receptors Ahlquist referred to Sir Henry Dale who, in 1936 together with Otto Loewi, won the Nobel prize of medicine for his findings on the chemical transmission of nervous stimuli.

Dale had taken up the receptor concept from Paul Ehrlich and he applied this concept to the adrenergic system.

Paul Ehrlich defined the receptor concept in laboratory work in 1913. This side chain theory was already contained in main features in Ehrlich's doctor dissertation of 1878. The leitmotif of his research work in the laboratory was « Corpora non agunt nisi fixata » and this was indeed to lead from a stain to an effective drug!

According to Ehrlich, chemical compounds have a selective pharmacological effect, if they bind to tissue as special cells. Within the cell, there are side chains having the function of taking up elements from blood circulation and to transport them into the cell.

He called these side chains also receptors and here, he developed his side chain theory which is not only related to drug effects, but also defined toxin-antitoxin concepts. Ehrlich projected this onto tetanus toxin. According to Paul Ehrlich the drug had to fit in its biological receptor like a key into the keyhole. This was a very good model as working hypothesis and formed the basis of chemotherapeutic development activities.

However, John Langley was the first to give an explanation for what could be the receptor concept. In 1905 he further explained the receptor concept in order to make clear the curare effect at the striated skeletal musculature. Langley distinguished between « chief substance » and receptive substance. This receptor theory established itself between 1920 and 1934 on a purely quantitative basis with Clark and Gaddum. According to them, the intensity of pharmacological effects is
directly proportional to the number of receptors occupied by the drug. Today we use radioactively marked substances in the laboratories to determine the number of receptors.

The first unspecific beta-receptor antagonist with a chemical constitution similar to that of the beta-receptor antagonist isoproterenol was dichloriso-proterenol (shortly DCI) developed in 1957, the modified beta-stimulating isoprenaline molecule where the two hydroxyl groups at the phenol ring were substituted by chloric atoms. Its mode of action was first presented at a symposium of the Federation of American Societies for Experimental Biology in Chicago 1957. In 1958 Powell and Slater published more precise research results of the Lilly research. Ahlquist's classification of alpha- and beta-adrenergic receptors was consolidated by DCI on a solid experimental basis. DCI served as prototype for the development of other adrenergic blocking agents. However, an intrinsic stimulating effect of DCI was unwanted and made therapeutic application and extensive clinical trials almost impossible. In animal experiments in dogs a depressor effect on the heart was shown after high DCI doses.

DCI was followed by pronethalol developed by the beta-blocker team in Alderley Park (Cheshire) at the British chemical company ICI. This substance was marketed under the trade name Alderlin for the treatment of angina pectoris, but was withdrawn after malignant growth had been observed in toxicity tests.

Further modification of the base molecule isoprenaline led to propranolol with a beta-blocking effect being 10 times that of pronethalol. In cooperation with Bert Crowther Les Smith synthesised the first pure INDERAL (the trade-name later used) in the ICI laboratories in Alderley Park in 1962. This was to present a further milestone in drug research of the last thirty years.

Propranolol was introduced into the literature by James Black and co-workers in 1964. One year later he presented results of a study comparing propethalol and propranolol. At the beginning propranolol remained a research product. In 1966 it was adopted in clinical medicine for the treatment of angina pectoris and cardiac arrhythmias. In 1967 Inderal was approved in the USA by the FDA for the indication cardiac arrhythmias and only in 1973 for the indication angina pectoris.

Until 1978 Propranolol remained the standard blocker. German doctors assumed a relatively reserved attitude towards this new therapeutic concept until 1973. At the beginning it was intended to use beta blockers only in special clinics and by experienced cardiologists and then only in a certain dosage determined with precaution. In this context cardiodepression probably played a role.

Overall, there were advantageous therapeutic perspectives for propranolol. Empiric data led to new clinical indications. Brian Prichard's observation of 1964 according to which propranolol had an antihypertensive effect even met with scepticism because there were at first neither a theoretical explanation nor pharmacological data. The longest delay in preparing data and obtaining approval by authorities can be illustrated at the example in the US. Only in 1976 registration approval was given by the FDA for propranolol for the indication hypertension.

The development of beta receptors entered a second phase with the findings on cardioselectivity. Research activities in the ICI laboratories were co-ordinated by Prof. Barrett in the years 1966-1970. It was the main aim to develop a beta-blocker without membrane-stabilising properties.

The decisive development work was done by a team of chemists (organic chemistry in eluding Hull, Le Count and Les Smith. In December 1968 it was possible to prepare ICI atenolol with the code number 66082.

The advantages of cardioselectivity lie in the molecular structure. There is an
oxypropanol-amine side chain and an amino group in para-position at the benzole ring. The lipophilicity of the molecule as a whole is deduced from this.

To conclude with I would like to remark that Dollery and Lewis were the first to have presented positive clinical results with atenolol in the treatment of hypertension. A cardioselective beta-blocker called practolol was marketed in 1975, but had to be withdrawn due to carcinogenicity and above all the oculomucocutaneous syndrome.

In September 1973 clinical trials with atenolol were first conducted in Germany with initial hesitation. Since mid-1976 it has been available under the trade-name Tenormin. With cardioselective beta-blockers a theory of knowledge was put into clinical efficacy. The search for more effective antihypertensive agents is tantamount to the development of an ideal beta-blocker.

II may briefly summarise some individual phases:

Individual phases until 1960 — this may be called almost a revolutionary phase — were followed by the development phase, a phase of evolution having as a result that today essential hypertension can be treated with a rational therapy regime. And in this context one may compare two things. On the one hand research work carried out in the university field and on the other hand research activities following World War II, namely that here the pharmaceutical industry gave essential impulses and developed substances which were introduced into the clinic.

To illustrate this the following remarks: Merck developed the thiazide diuretics, Lilly DCI in the US. Pronethalol and propranolol were synthesised in the laboratories of Imperial Chemical Industries in England, cardioselective beta-blockers such as atenolol at ICI UK and metoprolol at AB Hässle, Sweden.

During the 30 years of drug treatment of hypertension the beta-blocker became a « booster ».

I would like to complete this treatment concept and to show it in a historical perspective. This is a picture from the Medical Faculty of Mexico University. Its library contains books on pioneers in cardiology from Withering to Einthoven. My summary may perhaps be shortened as follows: The physiologists, pharmacologists and clinicians who have decisively contributed to the development of drug therapy of hypertension can be included in the row of pioneers in cardiovascular research. They converted pharmacologically interesting substances into therapeutically valuable agents, for the benefit of the patient, stimulated by hypotheses in drug design, armed with resources of the pharmaceutical industry and the experience and the mellowness of clinical medicine.