AN ATTEMPTED SYNOPSIS OF THE PHYSIOLOGY AND PATHOLOGY OF THE SYSTEMIC AND OCULAR ARTERIAL SYSTEM

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In the past 100 years, the educational structure of medicine has expanded as never before. Is there anyone at all still able to survey in its entirety, let alone able to have command of, the abundance of subject-matter which has been accumulated, or which perhaps has even overcome us? Let us admit that the answer is 'no', at least to the extent that today a *universitas litterarum medicinae* can no longer be attained by anyone.

A rapid increase of specialization results from this 'no'. It is certainly not my intention to belittle the admirable achievements of specialization, the mere existence of which is evidently justified by the success of brain and cardiac surgery, for example, or, within our specialized field, by the corneal graft.

In acknowledging this, however, we should not disregard the feeling of separation, and the impoverishment, arising from the loss of universality which formerly contributed much to the reputation of the medical profession.

Is there a Way out of this Dilemma?

I attempted to answer this question in my address at the centenary of the Deutsche Ophthalmologische Gesellschaft (The German Ophthalmological Association). In my opinion, no one more than the ophthalmologist is called upon to show that in a specialized field it is certainly possible to preserve thoroughly the unity of medical science. We do not want to be *'nothing-but-specialists'*, for

'Like all specialists, the ophthalmologists were reproached for isolating themselves from the rest of the medical field. Yet, from the outset, these remonstrances only applied to the degenerated kind of specialization which tends to forget that an organ is rooted in the entire organism and that its functions cannot be examined by someone unfamiliar with the system as a whole. But they do not affect those special fields of study which are reasonably founded on the groundworks of a broad natural science and which replenish the essence of this original knowledge with their findings.'

These were the words of Albrecht von Graefe almost 100 years ago.

In the preface of 'Kosmos', another great naturalist, Alexander von Humboldt, formulated his scientific conception as follows:

'What impelled me most was my desire to interpret the phenomenon of all physical objects according to their general coherence, and to regard nature as a whole, driven and animated by inner force.'

Today, in an era of continued specialization, this concept still holds true. I hope that with this thought in mind you will interpret the meaning of the topic I have selected; a topic that is to show you that the eye as an organ can only be properly understood as part of a whole system, or —in other words—that our specialized field cannot be mastered without knowledge of all other aspects of medical science.

The tempestuous development of the natural sciences and of medicine in the past 100 years has brought such a welter of new facts to light that it has become impossible for a single man to master all that is known about these subjects.

It is thus understandable that science, as it expanded, tended increasingly to split up into special fields. Nobody today will deny the value and importance of the individual branches of medicine. There is, however, a danger in training specialists who consider it their task to devote all their powers to the solution of a single problem. To narrow one's range of vision down to a single field of study that alone is felt to be interesting and important and to turn one's back on other branches of medicine is fraught with disadvantages for the development of the science as a whole. This danger can only be countered by relating the host of individual facts to each other with the aid of a comprehensive general view of the subject.

I should like to illustrate, by means of the topic chosen for this lecture today, how we can follow this road in ophthalmology as well, as it is a branch of study which likewise threatens more and more to become divided up into small specialized fields.

The choice of my subject today, however, was also governed by another reason. We are faced with the unnerving fact that the technological developments in recent decades have brought about radical changes in man's natural and social environment. These changes are to be held responsible for numerous diseases. It is therefore not surprising that we should experience a serious rise in the incidence of cardiovascular disorders in our modern industrial society. Life in large towns with its unprecedented acceleration of the speed of work, its artificiality, the deluge of stimuli produced by light, noise, radio and films, as well as many other circumstances have led to a change in man's nervous and psychic structure.

Consequently, the oculist, too, is compelled to concern himself, more than ever before, with circulatory diseases. He can, however, only understand the pathogenesis of a circulatory disorder in e.g., the retina, or optic nerve and initiate proper treatment if he constantly bears in mind the fact that he must regard the vascular system of the eye merely as a regional segment of the circulation as a whole which forms a closed functional system.

'The circulatory organs are admittedly governed by the metabolic requirements of the periphery, but the organism in general, with the aid of its neurohormonal regulatory devices which unite the individual parts into a whole, acts as a higher and thus influential principle' (Linzbach).

I therefore thought it would be an attractive task to try to give a synopsis of the systemic and ocular vascular systems under normal and pathophysiological conditions.

I realize that it seems presumptuous and is in any case, impossible to give an account in a short lecture, of all the known physiological processes and pathological changes in the vascular system. An added complication is that 'all our pathogenetic ideas are based either on circum-

stantial evidence derived from morphological findings, or on analogies inferred from animal experiments which are difficult to analyse' (Linzbach).

ARTERIAL SYSTEM

I shall now endeavour to describe the functional anatomy and pathological changes of the arterial system.

1. Circulatory physiology and pathology were held, until a few years ago, to be governed by the law demonstrated by Poiseuille at the Paris Academy, in 1841. This law postulates as an essential prerequisite a rigid, i.e. *non*-distensible bed along which the blood-stream flows. But the human being's vascular system consists not of rigid but of elastic tubes.

Let me explain the difference by means of a simple example: If water is drawn from a reservoir with the aid of a piston pump and the stroke volume is discharged into a rigid pipe, the water flows out of the end of the pipe intermittently with each stroke of the pump. This simple and practical pumping unit is uneconomical for the human organism. Each living cell requires continuous contact with the oxygen and nutrient substrates transported by the blood-stream. A periodic supply would not meet this elementary requirement.

It is therefore absolutely necessary that the blood-stream—as is in fact the case—should flow uniformly without showing a marked fall in pressure after each heart beat.

How can this process be explained physically? In elastic tubes, liquid, even when its delivery is intermittent, is made to flow continuously by the fact that only part of it moves in a longitudinal direction, while the rest distends the elastic wall and is stored there. After delivery has ceased, the distended tube contracts again, while the tensed wall exerts pressure on the liquid contained in it and forces it on. The result is a uniform movement of liquid in which only the volume injected each time is accelerated and not the total amount of liquid in the system.

The arterial wall, owing to its special structure, fulfils this mechanical condition in an ideal way.

Round the delicate endothelial tube are elastic lamellae and networks which, embedded into a 'basic substance' with the properties of a viscous gel (Buddecke), are compressed or expanded according to the state of contraction of the longitudinal and circular muscles. In the vessels near the heart, particularly in the aortic arch, the elastic portion predominates in the vascular wall while it gradually decreases towards the periphery in favour of the muscular portion.

At each heart beat the aortic arch is blown up like a balloon. It stores, as it were, a large part of the blood injected in systole, in order to deliver it during diastole. Stored potential energy is thus transformed into kinetic energy.

The storage ability of the aorta is called the *Windkessel* (or air-chamber function). I must briefly explain this term which has been adopted generally by all physiologists.

The German word *Windkessel* comes from the old fire engines. In these, the water was first pumped into a chamber filled with air. The air inside was thus compressed. In the interval between each pump stroke the air expanded and caused the water to flow out of the hose in a steady stream.

The rhythmic, pulsatory oscillations of the arterial wall are thus made possible by the latter's contractile, elastic elements. Nevertheless, an abrupt fall in filling pressure would occur after every systole. If, however, such a system includes a resistance in the form of a nozzle, the variations in pressure are substantially better balanced.

A 'peripheral resistance' adapted to the pump rhythm and delivery volume is therefore located in front of the capillary bed in order to ensure an optimum adjustment. This resistance is formed by the smallest arteries and arterioles; it also has the task of regulating the flow of blood to meet local requirements at any given moment.

Since the peripheral resistance does not constitute a rigid nozzle, but is elastic and can therefore vary in response to pressure, it offers other advantages which are important from the point of view of haemodynamics and energy:

(*i*) A fall in pressure in the air-chamber increases the peripheral resistance owing to passive constriction of the nozzle and thus slows down the flow from the pressure-storage vessel. The interval of rest for the heart is considerably lengthened, and the pressure in the storage vessel falls more slowly than in the case of a rigid nozzle.

(*ii*) Over-expansion of the air-chamber is prevented, since when the internal pressure is elevated, the peripheral resistance is passively reduced with the result that a greater volume flows away per unit of time and the wall tension of the air-chamber cannot be raised excessively.

(*iii*) The system as a whole regulates itself in such a way that fluctuations in the 'basic pressure' (diastolic pressure) are kept to a minimum; this regulation is largely independent of the delivery volume (*SINN*).

2. In addition to the haemodynamic, mechanico-physical factors which ensure a continuous movement of the blood, there are also intravasal chemico-physical forces to be considered. The task of these forces is to pass the substances and gases transported by the blood-stream through the vascular wall. This exchange of substances takes place, as we know, in the capillary bed.

On the arterial side of the capillaries the blood-pressure is 30 mm.Hg, whereas the oncotic pressure of the macromolecular proteins is only 23 mm.Hg. There is thus a difference in pressure of 7 mm.Hg. With the aid of this filtration pressure the solutes in the blood (minerals, fats, sugar, etc.) are forced through the capillary wall into the surrounding tissue. Oxygen, which is fixed to the haemoglobin of the red blood corpuscles, escapes chiefly by diffusion.

In the capillary segment between the arterial and venous sides the blood pressure has fallen to 23 mm.Hg and is thus in equilibrium with the pressure of the blood proteins. Consequently, no exchange of substances takes place in this 'neutral zone'.

On the venous side the blood pressure continues to fall. As a result, the oncotic pressure predominates and sucks the degradation products of metabolism into the capillaries with a force of about 7 mm.Hg. At the same time, CO_2 diffuses from the tissue into the capillaries.

I have intentionally chosen a U-shaped capillary as an example, because syphon-like arches are characteristic of the retinal capillaries. They enclose the abovementioned 'neutral zone' in which the flow-velocity of the blood reaches its minimum. The O_2 tension of the blood is at its lowest here, while saturation with waste substances is at its highest. This explains why disorders in this capillary sector are common in cases of diabetes mellitus.

3. I turn now to the physiology and pathology of the peripheral arteries.

Let us begin once again with the functional anatomy of this segment of the vascular system and consider the following questions:

(*i*) How is the arterial wall nourished?

(*ii*) How are substances transported within the arterial wall?

(*i*) It is fully agreed that the vascular walls—which are comparable in structure to the retina—are supplied from an inner and outer stream of nutriment. The inner layers of the wall are nourished by diffusion from the lumen, and the outer layers by the vasa vasorum. The layers of tissue at the boundary of these 2 supply areas constitute a 'critical zone of nutrition' which, as we shall see later, may become a collecting point for waste products.

I have to limit myself to this short reference. A detailed description of the chemical composition of the arterial wall and of the metabolic performances of the individual cell of the arterial wall which, e.g. are highly interesting for the understanding of the biochemistry of arteriosclerosis, would exceed the scope of this lecture.

(*ii*) The transport of substances within the arterial wall is governed, according to Linzbach, by the following forces:

(*a*) The osmotic concentration gradient between the blood, the cytoplasm of the endothelial cells and the subendothelial connective tissue. All the substances dissolved in the blood, including oxygen, can pass from one space to the other by diffusion, provided the inner and outer membranes of the

endothelial cells are permeable to these substances and the latter are not consumed by the endothelial cells themselves.

Endothelial cells and subendothelial cells (subendothelial polysaccharides) act in a way as a 'molecular filter'. Smaller molecules (amino-acids, glucose, electrolytes) pass the blood-tissue barrier according to the laws of diffusion and osmosis. Increasing molecular size implies inhibition or complete prevention (β_1-lipoproteins) of the passage. The molecular shape and the measurements of the endothelial cell correspond to the real proportions; electronic optic pictures, however, reveal a multiform 'interlocking' of the endothelial cells with each other (Buddecke).

(*b*) Active transport by the endothelial cells with the aid of the so-called cytopempsis of Moore and Ruska.

This cytopempsis is caused by the fact that small depressions containing portions of blood plasma arise on the inner surface of the endothelial cell. These depressions project into the interior of the cell, are strangulated, pass through the cytoplasm of the endothelial cell in the form of vacuoles and are given off to the subendothelial connective tissue.

(*c*) Capillary attraction is the third active factor in the transporting of substances. Since the lateral boundaries of the endothelial cells in the arteries are close together but are not joined by intercellular cement, there is a possibility of a film of liquid being sucked through these fine intercellular gaps owing to the movements of the pulse wave and filtered off into the intima.

(*d*) Filtration pressure. This, in principle, only comes into play on the other side of the endothelial membrane; it acts in a radial direction through the media and longitudinally through the intima.

4. Under what conditions is the nutrition of the vascular wall disturbed or the transport of substances within the vascular wall impeded?

We can divide arterial diseases into 2 major groups by distinguishing between structural changes in the vascular wall and functional circulatory disorders.

Included among the structural changes are vascular wall diseases characterized by hyperplastic degeneration or by inflammation. Functional circulatory disorders are chiefly the result of failure of the contractile elastic system.

ARTERIAL DISEASES

1. The Structural Changes in the Vascular Wall

(*a*) A site of predilection for hyperplastic degeneration is, for example, the aortic arch. The external arch of the vessel becomes diseased because the volume of the blood ejected during systole is reflected against it. Even in infants and small children we find here fatty, focal thickening of the intima and splitting up of the lamina elastica intima as a result of excessive strain on the vascular wall. With increasing age and particularly by the long-lasting existence of hypertension, small cavities (so-called 'Kriblüren') are formed. The latter develop at the site of contortion of the vessel, obviously on account of a lesion of the adjacent tissue by the hammering effect of pulsation in such a way that the vessel constantly tries to stretch under the impact of the (hypertensive) pressure wave. Thus an essential component in the strength of the arterial wall is abolished, namely the counter pressure of the tissue (Zülch). On account of this weakness of the wall, a rupture can take place in small vessels (as I shall still demonstrate in the course of this report), while deposition of acid mucopolysaccharides may occur in larger vessels.

The same process is also seen at other haemodynamically unfavourable sites, such as, in particular, the points where arteries originate or divide. A typical example of a 'pressure sclerosis' caused by the pressure and thrust of the blood is found at the bifurcation of the common carotid artery.

Because of the turbulence of the blood-stream at this particular site, the endothelium is subjected to excessive mechanical strain (Hess). It can be imagined that, like in the internal elastic membrane, very delicate tears and cracks will also develop in the tender endothelial layer which can no longer be sealed by the damaged endothelial cells. The endothelial barrier becomes insufficient and thus facilitates the invasion of plasma substances from the blood into the vessel wall.

All of you are familiar with the clinical picture which is brought about by a stenosis, or an obstruction of the internal carotid artery. The most frequently encountered localization is just above the bifurcation of the common carotid artery (Pichler, van de Weyer and Buhl).

In addition to this mechanical over-exertion of the endothelium in the area of the corresponding lesser curvature of a vessel, other factors have still to be taken into consideration.

The endothelium is covered by a broad, slowly flowing marginal stream of plasma and protein. With the latter, toxins, allergens and bacteria, for example, are brought along and find the opportunity to settle in the area of the endothelial contact ridges.

Presumably these noxious agents invade the tissue by a trans-endothelial approach according to the principle of cytotempsis described above, inhibit the cellular respiration and bring about an oedema. On account of the spreading of the oedema, the endothelium distends and a communication results between the main blood stream, the marginal plasma stream and the subendothelial intimal mesenchyme.

If one, furthermore, bears in mind that there are no erythrocytes in the marginal plasma-protein stream, it is quite conceivable that in case of a particularly broad marginal stream the endothelium will suffer from O_2 deficiency and that the insufficiency of the endothelial barrier would therefore be the immediate consequence of a hypoxia of haemodynamic origin. The processes which led to the lesion of the endothelium are thus of a complex nature.

Through the oedema in the mesenchyme—no matter whether the latter is brought about by mechanical, toxic or hypoxydotic factors—the stretching apparatus between muscle fibres and elastic fibres which has been established by Benninghoff at the border between intima and media, will certainly become relaxed. The unfolding of diffusion spaces thus caused, as well as the decrease of pressure in the intima the so-called 'Steigrohreffekt' or lift-tube effect favours the accumulation of colloidal substances (Linzbach).

Apart from this sclerosis which is brought about by reflection of the pulse wave at the inner vessel wall, we still know a type of sclerosis which is caused by extrinsic pressure (for example by a bullet or bone splinter). Because of the cicatricial fixation of the foreign body at the vascular tube or in its immediate environment, the longitudinal movements promoting the intramural fluid-stream which are synchronous with the pulse and the vibrations of the vascular tube are strongly inhibited or entirely abolished. In this way, the prerequisite for a localized lesion of the vessel wall is provided.

Particular sites of predilection for the described localized lesions of the vessel wall are furthermore encountered at the so-called 'physiological narrow sections', through which vessels (often accompanied by nerves) pass.

From comparative anatomy and from clinical observation we know of several instances in which arteries, while passing through such physiological narrow sections—also called 'tunnels' in bibliography—experience a certain compression even under normal conditions. At these narrow sections as well as in the presence of congenital anomalies, pathological changes of the vessel wall could supervene in the course of life which lead to a deficient blood supply of the area supported by the vessel.

The vertebral artery which after its origin from the subclavian artery climbs at first straight through the foramen transversarium from the 6th cervical vertebra up to the epistropheus vertebra, shows in its further and very short course until the entrance into the skull 3 strongly-curved windings. In this area, severe degenerative changes can occur already at an early date, like in the arch of the aorta. The artery furthermore has to pierce the capsule of the atlanto-epistropheal joint as well as the atlanto-occipital membrane.

The slit-shaped openings in both of these solid membranes constitute in a way, narrow sections for the artery, through which an inhibition of its pulse-synchronous movements and congestions of the intramural fluid stream are likely to occur.

In this connection, it is of interest to learn that measurements of the retinal arterial pressure in normal persons reveal a legitimate divergence of the values between the right and the left side. On backward and sideward bending as well as on torsion of the head, the retinal arterial pressure increases considerably at the side of bending. Bärtschi attributes this difference in pressure, first of all to a slowdown of the blood supply from the vertebral artery into the arterial circle of Willis, an opinion which had already been advocated by Gegenbauer years ago.

The subclavian artery. Furthermore, we know the narrow passage of the subclavian artery through the posterior scalenic hiatus (hiatus scalenorum). Here also anomalies may exist (for example cervical ribs, hypertrophic transversal processes of the 6th and the 7th cervical vertebra, muscles and ligaments) which could compress or displace the vessel as well as the plexus. The consequences are again disturbances of the blood supply which are known under the term scalenus anticus syndrome according to Naffziger.

The femoral artery. As a last example, I should like to mention the femoral artery. By means of serial arteriograms from the lower extremities in persons with vascular diseases, as well as on account of postmortem arteriographic demonstration of the femoral artery in persons who had not been affected previously by vascular diseases, Judmaier was able to establish that isolated changes in the adductor canal are present already in juvenile and middle age. They manifest themselves by indentations which are visible in the arteriogram. The study of vessels from deceased persons showed that the femoral artery is indeed narrowed by the vasto-adductorial membrane. By splitting of the said membrane and of the tendon of the adductor magnus muscle, the artery can be relieved from the pressure and the blood supply again improved.

I have purposely given particular consideration to some lesions of the vessel wall brought about by pressure, as I believe that similar physical factors are also likely to be responsible for circulatory disorders in the central retinal artery and in the nutritive vessels of the optic disc.

If we study first of all the course of the central retinal artery, we are struck by the fact that this vessel describes an arch both at its entry into the optic nerve and at its exit from the physiological excavation. It is perfectly conceivable that at both of these arches the vessel wall suffers a lesion and an impairment of its function—in the aforementioned way—by reflexion of the pulse wave.

Conditions comparable to the example just mentioned are found in the brain. The haemorrhage into the brain mass which constitutes the most frequent cause of the apoplectic attack, is brought about by rupture of the strio-lenticular artery (haemorrhage into the corpus striatum). The haemorrhage takes place at the knee of the artery which bends at a right angle. In old people, this knee is often affected in addition by ectasia. Moreover, the risk of haemorrhage is particularly high on account of the fact that the strain on the vessel wall in transverse direction is especially strong in the knee, as the vessel tries to stretch under the effect of the haemodynamic pressure wave. If the supported tissue is furthermore highly dependent on oxygen, as it is the case in the putamen and in the retina, hypoxia and accumulation of acid metabolites would rapidly take place (Zülch).

Let us recall in addition that the central retinal artery passes through the rigid openings of the lamina cribrosa, which become constricted by the increase of connective tissue in the course of ageing. Thus we find at this particular site all the prerequisites for a pressure sclerosis.

If a gradually increasing constriction of the lumen of the artery takes place in this 'lamina cribrosa tunnel', a 'deficient blood supply' of the retina results from a slowdown of the blood-stream. In analogy to coronary and cerebrovascular insufficiency (Corday), this condition could also be called retino-vascular insufficiency. We know the various sequelae of hypoxaemia and hypoxia as dyshoric spots, senile pigmentation and depigmentation, cystoid retinal degeneration and retinal detachment that frequently develops from the latter. (Similar haemodynamic conditions are obviously also found at the so-called crossing points of arteries and veins.)

The clinical picture takes a more dramatic course, when the retinal blood supply is not gradually diminished, but acutely interrupted. In this instance, we see on ophthalmoscopic examination, a milky oedema of the retina with very constricted, almost bloodless arteries, a picture which we are accustomed to call 'embolism of the central retinal artery' in clinical terminology. This expression, however, is not exact, as an occlusion of the central retinal artery is much more frequently brought about by a thrombus which has grown at a pathologically altered wall of the blood stream (arterial thrombosis) than caused by an embolus washed into the blood stream.

At first, the interpretation of the acute occlusion of the lumen in arterial thrombosis seems to be difficult. The

prerequisite for the formation of a thrombus is thought to be an alteration of the intima. Müller and Otto were able to prove conclusively in a model experiment that whirlpool streams occur beyond side connections which branch off at right angles. This explains, for example, the favourite localization of coronary thromboses in the area of the ramus descendens of the left coronary artery below the point of separation of the ramus circumflexus. Similar haemodynamic conditions should also arise, when an intima pad protrudes into the vascular lumen.

Aschoff has already demonstrated many years ago that whirlpool streams that favour the development of a thrombosis develop in the 'shadow' of the blood-stream behind the protruding intima pad. As long as blood pressure and speed of the blood-stream are geared to the requirements of daily work in hypertensive and arteriosclerotic persons, i.e., as long as both of these components are high, respectively accelerated, the possibility of a rapid increase in the size of the precipitation thrombus is only remote. If, however, the physiological nocturnal decrease of the blood pressure and the slow-down of the pulse take place in these patients, the pressure and the speed of the blood-stream will also diminish. A thrombus which narrows and occludes the vascular lumen can therefore develop within a short period of time. Thus we can also find the explanation for the clinical observation that patients affected with hypertensive and sclerotic diseases will suffer a cerebral attack (Zülch), respectively complain of stenocardia and lower leg pains often in the early morning hours (mostly between 2.00 and 3.00 a.m.) when the regulation of the cardiovascular system by vagus influence is most prominent, or that these patients notice the severe impairment of their visual function on awakening in the morning. These facts should be a warning to every physician not to lower the blood pressure in sclerotic hypertensive persons excessively and abruptly by drug therapy, particularly not during the period of night rest.

Let us now deal with the nutritive vessels of the optic disc. Contrary to the central retinal artery which (as is well known) does not have anastomoses under physiological conditions, these anastomoses are preponderant in the area of the papilla and the lamina cribrosa. A survey of the vascular conditions in this area is rather difficult. Undisputed is the existence of the circulus arteriosus sclerae (Zinnii s. Halleri) and of its anastomoses with the proper vascular system of the lamina cribrosa. The latter consists of a dense network of most delicate vessels; they are thought to branch off from the central retinal artery which (as is known) does not have any branches from its entry into the optic nerve up to the lamina cribrosa. Also the branch of the central artery of the optic nerve (François and Neetens) which runs towards the papilla has to be regarded as a rather considerable supply vessel for the prelaminar and the retrolaminar areas. Nowadays, laminar-chorioidal, chorioidal-scleral and pial-scleral anastomoses are still known besides the already mentioned anastomosis between the arterial circle of Zinn and the laminar network.

Again we can distinguish a chronic deficient blood supply from an acute nutritive disturbance of the papillary tissue.

The typical example for a chronic deficient blood supply is the slow atrophy of the papillary tissue with development of a flat excavation in the senile age period. This condition can be attributed to a so-called 'death from hunger' which we encounter likewise in arteriosclerotic renal scars and in granular atrophy of the cerebral cortex. It is typical for a chronic circulatory disturbance that the function of the involved tissues remains preserved or only slightly diminished for a long period.

Contrary to this kind of chronic circulatory disturbance, one can observe a sudden and almost complete loss of function in the so-called 'death from suffocation' which is brought about by an acute interruption of the blood circulation in the nutritive vessels of the papillary tissue. The question, how—in spite of the possibility of a collateral circulation by existing anastomoses—such an interruption could happen, shall be discussed after the description of the ophthalmoscopic picture.

The visible consequences of a supply disaster in the area of the optic disc are the enormous swelling and pallor of the papilla. Siegert therefore calls the disease 'acute ischaemic papilloedema'. Kreibig speaks of an 'opticomalacia'; in the Anglo-Saxon countries the term 'ischaemic neuritis' is used. I believe that the term 'neuritis' is not quite correct, for there is no evidence of an inflammation. According to my opinion, the clinical picture in question is rather a typical 'ischaemic colliquation necrosis', an infarction of the papillary tissue.

On ophthalmoscopic examination, we see an extreme swelling of the optic disc. At the onset of the circulatory disturbances, the colour of the disc can still be normal; in most instances, however, it becomes conspicuously grey, but respectively pale at an early stage. The retinal arteries are visible, however mostly of narrower appearance than could be expected from the age of the patient. Occasionally, a branch of the central retinal artery becomes obstructed, so that the retinal area supported by this branch shows the swelling and the haziness described above. Small haemorrhages on or in the vicinity of the optic disc, belong also to the clinical picture. Within a short time, an extreme pallor of the optic disc develops as the symptom of an incipient atrophy. Generally also the other eye is affected sooner or later under the same symptoms. We find this clinical picture in advanced arteriosclerosis as well as in temporal (cranial) arteritis.

I should like to explain the ophthalmoscopic picture by referring to 3 case records:

(1) Paul R., 50 years old. General findings: essential hypertension and arteriosclerosis, BP 220/115 mm.Hg.
Acute papilloedema had occurred and was slowly regressing. Although systemic and local measures were taken immediately to promote blood flow, atrophy and amaurosis developed.

(2) Ludwig H., 63 years old. General findings: essential hypertension.
Acute papilloedema, retinal haemorrhages, vascular sclerosis, copper-wire arteries in the form of the Greek letter omega. Atrophy developed, with severe constriction of the arteries.

(3) Agnes O., 69 years old. General findings: essential hypertension, arteriosclerosis, BP 180 - 200/105 mm.Hg.
Both eyes became affected, the one a short time after the other. Papillary atrophy with blurred outlines had already developed in the first eye. The second eye showed, besides papilloedema, a vascular disorder of the retina in the form of a branch embolism.

With good reason we can compare the ischaemic colliquation necrosis from vascular occlusion in the papillary area with the acute ischaemic renal infarction and with *white encephalomalacia*. Also in these instances, the pathological features in question are a colliquation necrosis with swelling of the tissue.

It is perhaps appropriate at this juncture to discuss the physico-chemical changes that are undergone by the cell when the blood circulation is interrupted for any reason at all. These changes provide an explanation for the origin of papilloedema and its disastrous consequences.

A tissue cell which is adequately supplied with O_2 and nutrients, has a certain content of water, proteins, salts, etc. The cell thus has a certain volume and a certain osmotic pressure which is higher than that of its environment. This means that the cell endeavours to attract water. This, in turn, would lead to swelling and eventually to bursting of the cell, if nothing were done to remove the surplus water.

In order to maintain normal conditions, therefore, osmotic work is called for, that is to say, salts, which diffuse through the cell membrane in accordance with their concentration gradient, are actively pumped back with the expenditure of energy. In this way, not only the concentrations of the individual electrolytes, but also the water content and thus the volume of the cell are kept constant. In the intact cell the energy for this 'electrolyte pump' is provided by the known energy-supplying reactions of metabolism, i.e. respiration (O_2) and, to a lesser degree, glycolysis.

Where the oxygen supply is deficient, cellular respiration fails to provide any energy. Anaerobic glycolysis, which is an emergency function, can, however, only continue until the available stored substrates are used up.

Owing to the lack of energy, the active transport of electrolyte ceases. The electrolytes are evenly distributed between cell content and external medium. Water is bound to enter the cell which swells and dissolves.

The function of neighbouring capillaries can be impaired by elevated tissue pressure, so that more and more cells suffer from an insufficient supply of nutrients and O_2. A fateful vicious circle arises which can no longer be broken. This also applies to ischaemia of the optic nerve and explains why our attempts at therapy fail.

(*b*) The second cause of a structural change in the vascular wall is inflammation.

The conditions encountered following the lodging of a bacterial embolus in the vascular wall are straightforward and clear-cut. They therefore require no further explanation.

On the other hand, mention should be made of that type of arterial or capillary inflammation which is caused by the attack of a noxious agent from the outside, i.e. in the region of the adventitia.

Diseases with Obscure Pathogenesis

I shall name only 2 diseases which cannot fail to interest the oculist owing to their obscure pathogenesis: Periarteritis nodosa and Kyrieleis' discontinuous reversible arteriopathy.

Both these angiopathies are relatively rare, and both are characterized by localized involvement of the vascular wall. It is a moot point whether periarteritis nodosa can be perceived with the ophthalmoscope. Discontinuous arteriopathy, on the other hand, can be seen with this instrument, as I have been able to prove to my own satisfaction on numerous occasions.

Kyrieleis, who has given an excellent description of the clinical picture, supposes that it is brought about by a hyperergic reaction in parts of the vascular wall to allergens. These allergens spread from a uveal focus, that is probably of a bacterial metastatic type and is usually situated in the choroid membrane, and impinges on the arterial wall from the outside. The discontinuous, rhythmic distribution of the reaction foci over the arterial tube can be explained in the same way as other rhythmic formations in human pathology that are analogous to the rhythmic precipitations of colloid chemistry. It is furthermore probable that the vascular nervous system also plays a part.

I should like to draw your attention to this latter point in particular.

We know that the close connection between the nervous system and blood-vessels is due not only to the presence of an autonomic nervous longitudinal pathway, but also to segmental innervation. According to Stöhr jnr., the terminal formations of the nerves (the so-called terminal reticula) spread out not only at and in the muscle cells of the media, but also in the intima and adventitia. This suggests that each individual cell in the vascular wall is influenced by nerves. The network of nerves then extends continuously into the surrounding area, with the result that the organ cells innervated by the autonomic nervous system form, together with the arteries supplying them, an indivisible 'higher functional unit' (Linzbach).

We are doubtless entitled to put forward the hypothesis that every inflammatory process provokes vascular dysregulation of nervous origin which leads to spasm.

Corresponding to the segmental structure of the vascular wall's nerve supply, localized endothelial damage is caused by hypoxaemia and hypoxia. Plasma proteins can now pass through the loosened endothelial cell covering and penetrate deeply into the tissues, thus causing a 'tissue albuminuria', to use Eppinger's term. Overcharging of the lymph and pericellular spaces with plasma constituents, particularly the active complements (Fischer and Argenton) means, however, that the diffusion of oxygen, that is present in only inadequate quantities, is rendered more difficult. The neighbouring cells become anoxic and die. Proteolytic enzymes are activated as a result and the process continues in depth.

Owing to the already mentioned segmental structure of the vascular wall's nerve supply, circumscribed, nonspecific inflammatory reactions of the adventitial connective tissue occur. These, in my opinion, constitute the morphological substrate of the cuff-shaped deposits visible through the ophthalmoscope in discontinuous arteriopathy. I believe that allergens from remote inflammatory foci do not necessarily have to play a part in the origin of this arteriopathy.

Since the nerve supply to the veins too, is segmental in structure, it is not surprising that the same changes can be encountered in the venous wall as well.

2. Functional Vascular Disorders

Functional dysregulation of the vascular system is caused by hypertensive or hypotensive vascular crises.

(*a*) In cases of malignant renal hypertension, the diseased kidneys release renin (or hypertensin) into the blood. This vasoconstrictor substance is carried by the blood into all the organs, including the retina. The result is a condition that, in accordance with Volhard's suggestions, we usually call angiospastic retinitis.

Benign or essential hypertension can be either of central nervous origin or the consequence of endocrine dysregulation. Transitional forms of the disease are also found. The changes in the retinal vascular system are sufficiently well known.

(*b*) Hypotensive vascular crises may arise from a variety of causes. These include: trauma of the solar plexus, acute pulmonary collapse, acute heart failure (e.g., in infectious diseases), severe loss of blood (e.g., hepatic

rupture), etc. Arterial vascular disorders of the retina and optic nerve are among the frequent consequences of severe collapse. Since the picture is dominated by the systemic disease in these cases, the oculist is usually consulted only in an advisory capacity.

He has, however, a much more important task to perform in the second form of hypotensive vascular crises, i.e. in cases of postural or orthostatic collapse, also known as the vegetative-orthostatic cardiovascular syndrome.

Early diagnosis by an ophthalmologist can prevent some of the subsequent damage to the organism, that may be fraught with grave consequences. This is evidenced by the following observation.

During the last 2 years of the war and immediately afterwards we were surprised to find in Germany that we were being called in more frequently than before to treat *young* patients for sudden severe visual disorders or complete blindness. These patients had been working at their various trades or professions and did not feel really ill. It was only after careful general examination and circulatory function tests performed with up-to-date methods that the cause of the partial or total occlusion of the ophthalmic artery visible through the ophthalmoscope was discovered to be an orthostatic dysregulation. This dysregulation was probably due to the severe autonomic nervous strain and the malnutrition, especially protein deficiency, from which the population suffered in those days.

If we are to measure the consequences of a hypotensive orthostatic circulatory disorder, which is by no means as harmless as internists often assume (Sarre), we must first have some idea about the regulation of the blood pressure.

The level and constancy of the blood pressure are dependent on the efficiency of the heart, arteries, and arterioles. This efficiency can be assessed by determining the stroke and minute volume, the elastic resistance of the arteries, and the peripheral resistance of the arterioles.

At rest, stroke and minute volume, elastic and peripheral resistances, venous tone, and thus also the level of systolic (Ps) and diastolic (Pd) blood pressure are in equilibrium.

If a person who has no circulatory disease is placed on a tilting table and then moved *passively* into the upright position, force of gravity causes the blood to sink into the periphery. But this sinking of the blood is compensated for in only a few seconds by an increase in peripheral resistance. There is thus only a brief rise in diastolic pressure.

In the most common and most important form of orthostatic dysregulation, lack of venous tone results in the lower half of the body (splanchnic region) having an abundant supply of blood and the upper half an inadequate blood flow. The consequences are a diminution in the return flow of the blood to the heart, as well as a marked decrease in stroke and minute volume, thus causing a rise in diastolic pressure and a fall in systolic. A further consequence is arteriolar contraction.

The variety of symptoms in orthostatic hypotonia is frequently the reason for both erroneous diagnoses and treatment.

Among 100 patients who consult the physician for 'heart complaints', 15 suffer from orthostatic cardiovascular disturbances which constitute the actual cause of their complaints (Schmidt-Voigt).

The cardiac complaints consist of stinging heartaches and heart sensations up to pectanginous pains. Furthermore, cerebral complaints supervene. On sudden change of position, particularly when getting up in the morning, the patients complain of headaches, noises in the ear, fatigue from prolonged standing, as well as of visual disturbances that manifest themselves as flickering sensations in the eyes and finally as obscure vision. Moreover, attacks of vertigo up to unconsciousness and collapse can occur.

The orthostatic regulatory disorders demonstrated in human beings with the aid of modern methods for the study of circulatory physiology (to which I shall refer in greater detail when I describe briefly a few typical cases) were also observed by Meessen and co-workers in animal experiments. They, by forcibly holding a rabbit in the vertical position, managed to produce an orthostatic collapse in which the retinal vessels became severely constricted. A similar severe vascular disorder can also arise in other organs (e.g. heart, liver) as a result, for example, of histamine collapse.

The *results* of the circulatory analysis performed on our cardiac patients with the aid of the tilting table show that the systolic blood pressure falls in all cases, whereas the diastole rises. The stroke volume decreases, pulse rate increases, minute volume diminishes, but peripheral resistance rises.

The remainder of this address was illustrated by the projection of slides.