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Editorial

The Pathogenesis of Cardiac Infarction

A Few Comments on Some Unanswered Questions

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Summary. 1. Questions concerning coronary heart disease have been raised for more than 200 years, but the concept of coronary insufficiency is only 50 years old.

2. The pathological anatomy of coronary insufficiency is variable, unexpectedly rich and stratified, and full of pecularities.

3. "Coronary insufficiency" is the superimposed concept; "cardiac infarcts" and "inner myocardial layer damage" are subordinate.

4. The logical connection linking all the morphological consequences of so-called coronary insufficiency is the elective necrosis of the parenchyma. The anatomically demonstrable equivalents of coronary insufficiency are, from the point of view of coronary perfusion, the result of an inadequate "vis a tergo".

5. This principle is enshrined in a complex of conditions which has to be disentangled if an individual case is to be analysed. The complex comprises three sets of factors:

(a) the critical narrowing of the lumen of the coronary arteries and all their branches leading to a given territory;

(b) the weight of the functioning mass of the cardiac muscle;

(c) the cardiac effort required of the heart during the critical period of damage.

6. The presence of anastomoses between the coronary arteries is no proof of their functional efficiency or readiness in an emergency. The conditions which determine their responsiveness, particularly as far as time is concerned, are at the moment still not adequately known.

7. The behaviour of ions at the membranes of living cells, particularly of muscle fibres, is a fundamental phenomenon, fascinating in its primitive aspects. A disturbance of cellular respiration, produced in the cardiac muscle "regularly" by the "inadequate vis a tergo" of coronary perfusion, leads to an exhaustion of energy stores, and to an increased influx of calcium

* Dedicated to Professor Dr. Dr. h.c. Gotthard Schettler on the occasion of his 60th birthday (13th April, 1977)

ions. This activates the ATP-ase of the myofibrils, and thereby reduces the level of adenin nucleotides. This loss of energy-rich substances not only militates against the function of the muscle fibres, it also initiates their necrosis.

8. The cardiac infarct is a phenomenon of a disturbed circulation – a "dyscirculatory" change. It is found in certain sites of predilection, whose choice becomes intelligible only through an understanding of the developmental history of the coronary arteries. The cardiac infarct is "coronary-dependent"! There are, however, also *other* forms of, and possibilities leading to, the development of myocardial necrosis. The nosology of the cardiac infarct clearly distinguishes the latter from these other forms. In damage of the inner layers of the myocardium infarcts do not develop by the confluence of necroses of individual fibres or of groups of fibres. Infarcts are not a phenomenon of addition, they do not have the "character of a mosaic".

9. As in other tissues, in the human myocardium also there are lysosomes. They are found in hypertrophied muscle fibres. Topical relations to zones of necrosis have not been found.

10. Current views of arteriosclerosis applied to the coronary arteries as the main factor responsible for the myocardial infarct must be amplified by an additional consideration: If no account is taken of the relation between the tone of the coronary arteries and their filling, of possible spasms and paralysis, and of an inadequate homeostasis between these factors, the marked variability of the pattern of myocardial damage cannot be adequately understood. This "pathology of relations" must always be kept in mind.

Edward Jenner (1749–1823) knew, that his teacher John Hunter had complaints suggestive of angina pectoris. He observed the increasing intensity of Hunter's disease during 16 consecutive years. Hunter died in 1793. At necropsy Jenner found rigid coronary arteries with "concretions" and "coagulable lymph" – in other words, a stenosing sclero-atheromatosis. The world is indebted to Jenner not only for vaccination, *Jenner is also the father of the anatomic concept of stenosis of the cardiac vessels and its effects.* He had no doubt that the changes in the coronary arteries were the real cause of John Hunter's disease and death.

From that time on there has been a debate concerning the significance of the relations between:

the intensity and the extent of the changes of the coronary vessels	and	the nature and the degree of the changes of the cardiac muscle.

Cardiac infarcts develop in the unit formed by "circulation" and "myocardial parenchyma". In analogy to the hepaton, nephron, odonton or histion I have called this entity the "myocardion". It represents the conceptual unit of the myocardium with its accessory structures – the connective tissue, blood vessels, lymphatics, and nerves. It is obvious that the parenchyma in the strict sense of the word – i.e. the myocardial fibre – must not be examined entirely by itself. "Para-enchyma" is the tissue *beside* the pathways of the appropriate fluids. That tissue can only work properly if the "milieu intérieur" is intact. The

metabolic processes of tissue maintenance and of work performance are therefore also biotechnically linked to each other. The most vital expression of the activity of the cardiac muscle is its automatic contractility. If the development of an infarct is, therefore, to be explained, one has to look for those conditions that render impossible the "specific" vital manifestations of the myocardium. This becomes a problem of metabolism insofar as both the maintenance of structure and the performance of work are tied to very concrete preconditions of energy production. If the metabolism of maintenance and of performance could be covered by *fermentation*—phylogenetically the older form of producing energy—, it is probable that no parenchymal necrosis would develop even at the most pronounced degree of stenosis of the coronary arteries. Unfortunately, however, *all* our parenchymal tissues are dependent on the supply of oxygen, and the cardiac muscle *must* cover its energy consumption by respiration. It could otherwise neither perform work nor maintain its structure.

Looked at *that* way, but only *that* way, it can be said that necrosis of the myocardium is also determined by causes within the organization of the muscle cells! Logically one is compelled, however, to ask further what, *as a rule*, can disturb the supply of energy, in other words the supply of oxygen. The answere then must be: In the *first place* an alteration of the coronary arteries—vessels that have formed in the course of the complicated evolutionary development of all warm-blooded animals.

The *development* of the coronary arteries, in terms of the *history of the earth*, is exciting, because it is not free of circuitous routes and constructional weaknesses. It may be permissible to speak of a "constructional weakness" if, thinking anthropomorphically, one would like to see the functional integrity of the human heart preserved for an almost "unlimited time" (Doerr, 1972).

Disturbances of the energy supply of the heart are, therefore, spoken of as *coronary insufficiency*. For the last 50 years much work has been done to explain its causes and effects. The elucidation of the essential pathologic-anatomical features we owe to Franz Büchner (1939, 1961, 1970, 1973, 1975). Coronary insufficiency is essentially a problem of balance. Its morphologic equivalents vary. Coronary insufficiency is the overall concept; "elective parenchymal necrosis", "damage of the inner myocardial layers" and "infarct" are subordinate manifestations. Those forms of coronary insufficiency in which anatomical changes of the coronary arteries, no matter of what type, cannot be demonstrated, are called "relative"; in the presence of anatomical disturbances one speaks of "absolute" insufficiency.

This division is patterned after the conventional *rules* which have proved their value for the classification of acquired *changes* of the *cardiac valves*. Absolute valvular defects are determined by anatomical changes, relative ones, however, do not present gross distortions of the valvular tissue. There has to be, of course, a morphological pre-requisite in "relative" valvular defects and (coronary) insufficiencies: As fas as the heart valves are concerned, there may be changes at the margin of insertion, at the annulus fibrosus and in the extent of the "surface reserve" (of the valvular mesenchyme); as for the coronary arteries, there may be a decrease in the "Windkessel effect" of the ascending aorta, a high origin of the coronaries, a weakened contractility of the left chamber (by myocardosis, myocarditis, confluent necroses of groups of fibres). The inadequate *vis a tergo* is fundamental importance for the pathogenesis of coronary insufficiency.

In the Pathological Institute of the University of Heidelberg there were performed during ten consecutive years 12,747 necropsies; the average age at death for men was 58.5 years, for women 61,4 years. In this material there were 8837 cases with *accentuated* general arteriosclerosis; 7396 cases had sclerosis of the coronary arteries of *all* degrees of severity; in 1373 cases there was myocardial infarction, and 360 of these had more than one cardiac infarct. Occlusions of the coronary arteries with infarcts were found in 670 cases, without infarcts in only 14 cases. If one correlates, over the same time interval, the cases of cardiac infarction with the simultaneously demonstrated generalized and severe arteriosclerosis and, as controls, compares another group of diseases – for example all instances in whom the cause of death could not be attributed to a cardiac infarct, but to a malignant tumor, – one can then recognize without difficulty that there is an association between arteriosclerosis and cardiac infarction, and that malignant tumors and arteriosclerosis have nothing whatever to do with each other. These correlations are becoming even more apparent if one takes note of the simultaneous occurrence of stenosing sclerosis of the coronary arteries in cardiac infarcts on the one hand, and in instances of malignant tumors on the other. One can then also see that in women, who die of fatal cardiac infarcts, the stenosing sclerosis of the coronary vessels is not as commonly demonstrated as it is in men. Perhaps in women factors other than coronary also play a role in myocardial infarction. In recent years much emphasis is being placed on the significance of *coronary thrombosis* for the development of an infarct. *We* have found coronary thrombosis in only 20% of all deaths with infarcts. The number of cases showing coronary thrombosis has remained reasonably constant during ten years.

The work-up of our material, on which these considerations are based, has yielded certain *rules of thumb*, which are briefly listed here:

1. The bigger the cardiac infarction, the more frequently one can find an occlusion of the coronary arteries. Transmural infarcts almost always show such an occlusion; in other words, they present as a rule a more severe sclerosis *with* thrombosis.

2. Medium-sized ("banal") cardiac infarcts show in more than half the number of cases no occlusion of the coronaries. In fewer than 20% parietal thrombi were found.

3. Infarcts without occlusion of the coronary arteries I have called "infarcts without obturation" or "non-obturation-infarcts", (N.O.I.).

4. Malformations of the coronary arteries (e.g. the origin of one coronary vessel from the pulmonary artery), obstructions of the ostia (by dysgenetic intimal protrusions and bands), high origin of the coronary arteries (2 cm above the usual site), disruptive changes of the coronary arteries and, finally, embolic coronary occlusions were found only as rare exceptions.

The expression "*non-obturation infarct*" has been chosen faute de mieux, a case of a "bad word" for a "good cause". If the contractile force of the left ventricle is not sufficient to overcome a moderate stenosis of the coronary atery; if at a "high" origin of the coronary vessel the "Windkessel" effect of the senescent dilated aorta is inadequate and cannot safeguard the filling of the vessel during the diastole of the chamber; if during protracted shock or even during an orthostatic collapse the venous return of the blood is inadequate – then, under all these conditions, the coronary arteries are not only not concluded but, in the first place, little enters into them or, in other words, they are not adequately

perfused. It is then, therefore, not only not a question of the occlusion of one or both coronary arteries, but of a functionally adequate filling that has not been achieved in the first place. "N.O.I." are more common than has been assumed. "Pure" cases, i.e. cases without a critical narrowing of the lumen of the coronary artery, make up fewer than 10% of all cardiac infarcts. "Absolute" coronary insufficiencies produce *more* infarcts, "relative" insufficiencies produce *more* damage of the inner layers. Infarcts without obturation of the cardiac vessels are not just situated anywhere in the heart. They are found there where in the evolutionary history of homo sapiens there once were two accidental "pipelines of oxygen" (Doerr, 1972).

One of these was derived from the vascular plexus of the foregut and reached the atrio-ventricular border via the dorsal mesocardium. The other pathway was formed by the arteriae mammaricae internae, and entered as a "caudal" cardiac band into the apex of the heart. N.O.I. are found in the dorso-basal or ventro-apical regions of the heart. They can be compared to the border zone infarcts of the watershed region of the neuropathologists. Why these two additional carriers of oxygen have disappeared, we do not know. From the evolutionary point of view the right chamber of the heart is the older one, and is better supplied by the coronaries; the left chamber is a more recent acquisition and hence at a disadvantage. Our heart shows features of the so-called heterochrony. This is one of the fetters of the somatic development of man, and little can be done to change it (Doerr, 1975b for literature).

Coronary insufficiency is caused by the following complex of conditions:

1. A critical narrowing of the lumen of all coronary arteries leading to a given territory.
2. The size of the heart, in other words: The weight of the "functioning mass" of the myocardium.
3. The demands placed on the heart at any given time.

Who, for whatever reasons, has a hypertrophied heart can develop an infarct even if the stenosing coronary sclerosis and the functional demands on the heart are only moderate. The person with a heart of normal weight (4 promille of the body weight) can afford a somewhat more pronounced coronary sclerosis without developing an infarct. A psychomotor load on the eutrophic myocardium will in all probability not produce coronary death, in contrast to the hypertrophied myocardium, when death may occur much more easily. In actual pathologic-anatomical practice conditions and problems are, of course, much more complex, and each individual case has to be carefully and thoroughly analysed on its own merit. A knowledge of the patient's history is essential also for the pathologist (Rössle, 1931). It is unfortunate that the study by Albert Dietrich (1935) is today already forgotten. In it he analyses an individual instance of fatal "coronary heart disease" having taken place in bouts. I would particularly like to draw attention to this treatise, because it shows in an *exemplary* manner, how only a *mode of thinking* which takes into account all the conditioning factors—in my opinion a specific methodological feature of special pathology—is commensurate to the difficulty of the topic: What else we have learned from Dietrich, and what we should not forget, is the emphysis on thinking in terms of relations. This approach supplements morphological pathology by a pathology of relations (Ricker, 1924, Nordmann, 1933). The *disturbance of function* of the *terminal vascular bed,* the question of synapses (Keatinge, 1966), the subject of neuro-transmitter substances (Meessen, 1968), in other words the sum of structural and functional events, offer a key to a proper understanding of pathogenesis.

The Following Actual Questions Merit Some Consideration:

1. Anastomoses between the right and left coronary vessels.
2. The determination of the age of thrombi.

3. Instantaneous death (Sekundenherztod).
4. The significance of lysosomes for the development of cardiac infarcts.
5. The cardiomyopathy of electrolytes and steroids.

Ad 1

It is well known that G. Baroldi, to put it in a simplified manner, has developed the concept that disturbances of the coronary vascular system cannot be the cause of the development of a cardiac infarct (1965, 1973, Baroldi and Scomazzoni, 1967), at least not on their own. He was led to this conclusion because he succeeded in demonstrating post mortem, by a specially developed technique, also in instances of cardiac infarction a dense anastomotic vascular network in the heart. To this one has to say:

a) One can certainly be impressed by the abundant number of anastomoses, if one seriously sets out to demonstrate these "cross-connections".

b) There is, however, a difference between the demonstration of anastomoses post mortem and the assessment of their functional significance in vivo. It is not a question of whether anastomoses can gradually develop and become functional, but entirely a question of whether they are also in an emergency fully functional, in other words, wheter they do respond.

c) Since Julius Cohnheim (1872) we are cognizant of the "factor of time", that means of the "coming and going" in the vascular bed past the site of occlusion; from the time of Ricker (1924) and Illig (1961) we are also aware of the particular mode of reaction of the terminal vascular bed after a sudden interruption. (Stasis *despite* the existence of anastomosis-like cross-links.)

d) The works of Schaper and Schaper (1971, 1974, 1976) have made it plain that *time* is always required for all the compensatory mechanisms to come into play. This may be a question of days and weeks, not of minute or hours.

e) If Baroldi's views are correct, infarcts should not develop for circulatory reasons in other organs either. To give only *one* example, mesenteric infarcts occur in a tissue with many anastomoses – problably more that are present in the cardiac muscle. I would like to emphasize already at this stage that the autodigestive (tryptic) pancreatitis does not represent an infarct and that, conversely, pancreatic infarcts do not represent tryptic pancreatitis.

The work of Baroldi is important and its results theoretically significant. His conclusions, however, are not of practical relevance as long as it is not possible to get all the anastomoses present to respond immediately after a critical stenosis of the lumen of all arterial carriers (to a given territory) has manifested itself. It is in *that field* that therapeutic progress could be looked for.

Ad 2

The question of how old the thrombi demonstrated in coronary arteries are is of supreme importance for a discussion of causal connections. I would like

to emphasize: The *tertium comparationis* for the association of factors (critical stenosis of the lumen, heart weight, cardiac work) cannot be "thrombosis or no thrombosis" but it can only be "the narrowing of the arterial cross-section"! In the effectuation of the latter thrombosis *can*, of course, participate. The formation of a thrombus may be decisive for a "crisis", it can be a concomitant phenomenon, but it can also be superimposed. I have found thrombi of all ages in the coronary arteries of myocardial infarcts: Old organized thrombi; thrombus formation in "bouts", with old thrombi showing recent stages; obturating thrombi which unquestionably preceeded the onset of infarction; but there were also thrombi which perhaps developed on the basis of swelling and necrosis of the wall of the coronary arteries, at about the time when the myocardial parenchyma was breaking down. Finally one can occasionally also find fresh thrombi which are quire obviously younger than the necrosis of the infarcts. We are studying the site of attachment of the thrombus with the electron microscope after the procedure of J.A. Rossner (1971). By means of comparative light and electron microscopic studies one can then establish: The periodicity of the fibrin layers, the preservation of the individual thrombocytes and of the other formed elements of the blood suspended in the network of fibrin, the state of the endothelial cells, the abundance and density of the sedimented cellular debris, the beginning regeneration (organization) on the part of the adjacent endothelial, connective tissue and smooth muscle cells. Although Rossner's technique is very time-consuming, its results are so excellent that they have enabled us to view the thrombosis occurring within the framework of the pathogenesis of cardiac infarcts as a secondary phenomenon.

The statement, that in a myocardial infarction the thrombosis of the altered coronary arteries is a secondary phenomenon, does under no conditions imply that the formation of thrombi is unimportant. *Every* effort should be made at an efficient prevention of this happening, unless there are valid reasons against it. The thrombosis of the coronary vessel acts as a determining, accentuating and aggravating factor, but it does not "fall out of the heaven", it does not develop "somewhere", it has a "history of its own", and with Aschoff I can, in opposition to Dietrich, say: The thrombosis is a phenomenon of the blood, and not of the endothelium.

Ad 3

In 1917 Heinrich Ewald Hering (the Younger) published a monograph on the "Sekundenherztod" (instantaneous cardiac death), which is still well worth reading today. He emphasized that although in instances of sudden cardiac death one can find anatomical changes, these changes are not sufficient to explain the suddenness with which death occurs.

We have by now learned more about the events of sudden death from natural causes (Doerr, 1972), and although we can be certain that even in the critical places of the coronary supply of the specific myocardium there are not present adequate changes (Doerr, 1975), there still remains a residuum of observations which makes it difficult for us to say clearly what the immediate cause of death may have been.

On the 13th of August, 1975 the body of a man aged 51 years, was very carefully examined (SN 815/75). This patient had been admitted to the Medical Clinic of the University of Heidelberg

that morning for the study of "liver damage" of an unspecified nature. Before any investigation could be undertaken, he collapsed early in the morning while performing his toilet. He was instantaneously seen by a physician who diagnosed cardiac arrest (asystole). At necropsy the body weighed 60 kg and the heart 400 grams; there was a finely nodular cirrhosis of the liver (1,550 g); although the patient was known to have suffered from mild diabetes mellitus, there was no significant arteriosclerosis. The coronary arteries showed only sclerosis of a minor degree and appeared, if anything, more rigid-dilated. The sinus node and the AV-system showed sclerosing fibrosis without recent changes. Only the walls of the arteries in the carotid sinus showed somewhat more pronounced changes. Here one could find an eccentrically stenosing (but not occluding) atheromatosis free of thrombi. The glomus caroticum showed no pathological changes.

I must consider this case as an example of instantaneous cardiac death, for which I have no satisfactory explanation. I *assume*, however, that such an instantaneous death can occur by the simultaneous failure of the sinus and the AV nodes, perhaps under the influence of a crisis of nervous regulations. This, however, is only an *interpretation*, not an explanation.

Ad 4

Manfred v. Ardenne (1971, 1972, 1973, 1974) has repeatedly suggested that the cardiac infarct may be a consequence of a lysosomal chain reaction. Provoked by perhaps only a moderate deficit of coronary perfusion autodigestion may set in, which can lead to the appearance of an infarct-necrosis.

This thesis would be new as an explanation of the pathogenesis of cardiac infarcts, although it is old for disorders of other organs. One can indeed observe that in certain forms of experimental pancreatitis there appear in the epithelial cells of the acini, at a distance from the site of action of the stimulus, vacuolar lysosomes, the "suicide bags" from which are liberated active enzymes causing auto-digestion (Doerr et al., 1965).

The cardiac muscle, however, is not an organ of metabolism of the type represented by the pancreas, and tryptic pancreatitis is not a pancreatic infarct (Becker, 1973, as opposed to Hranilovich and Baggenstoss, 1953).

It has, nevertheless, to be admitted that until a few years ago we were not certain that lysosomes do occur in the hypertrophied human myocardium!

My former Japanese collaborator Dr. Iwata has, in a systematic electromicroscopic study of small myocardial fragments removed during open heart surgery, demonstrated picturesque lysosomes. At that time Iwata was not aware of our problems and questions. His assignment was to collect material. At that time we wanted to get to know the electromicroscopic appearance of the *human* myocardium. Dr. Iwata followed our suggestions with admirable persistence and conscientiousness. All instances were cases of hypertrophied hearts, mostly with acquired valvular defects. Our material did not include hearts with infarcts or with ventricular aneurysms (Doerr et al., 1976).

M. v. Ardenne has incorporated our findings into his thesis – no agreement having been reached with us. My circle of collaborators has always emphasized that the occurrence of lysosomes in the hypertrophied muscle fibre is probably somehow associated with the self-cleansing efforts of the tissue which have been rendered more difficult by the hypertrophy. In favor of this assumption is the fact that the well-known basophilic degeneration of myocardial fibres (Liebegott, 1936; Doerr and Holldack, 1948, Linzbach, 1972) is always found when lysosomes become apparent, and vice versa. The occurrence of lysosomes

in parenchymal necrosis, elective necrosis of the parenchyma side by with lysosomes, we have so far not found!

Ad 5.

Are there necroses of the cardiac muscle which could be mistaken for the necrosis of infarcts? Are there myocardial necroses which are not determined by coronary insufficiency and which develop by other mechanisms?

Since 1958 Hans Selye (for references see Selye, 1970) has elaborated the concept of the "infarctoid cardiopathy" in rats. He distinguishes an electrolyte-steroid-cardiopathy *with* hyalinosis (ESCH). The necrotizing process can be increased by the administration of dehydrotachysterol, but decreased by giving potassium chloride. ESCH is determined by aldosteron, and is dependent on the sodium content of the diet. Later Selye (1972a) has shown that mineralo-corticoids given in excess cause hypokalemic necrosis, but that an inhibition of mineralo-corticoid production by the administration of spironolacton produces healing of necroses. Selye distinguishes "syntoxic" and "catatoxic" steroids. The former tend to inhibit the reactions of defence, and thus favour the development of necrosis. The catatoxic steroids, however, interfere with the action of the aggressors themselves, and thus would have a protective effect. *The* catatoxic protective substance is stated to be pregnenolon-16-carbonitril (PCN; Selye, 1972b), which has been tested in Selye's laboratory, but not in man.

These findings reported by Selye are rather difficult to understand and a discussion during the 56th meeting of the German Society of Pathology did not clarify them any further. Selye, it appears, does not make a distinction between "his" necrosis of the cardiac muscle and "our" infarct necroses. The work of Fleckenstein (1971, 1975) has yielded results which are more convincing to the pathologist. Fleckenstein (1967) has made a distinction between an insufficiency determined by "utilization" in the cardiac muscle, and an insufficiency due to a "deficiency". The former may develop by a competitive inhibition of the influx of calcium ions or by a mechanical interference with transport via the tubuli transversales of the muscle fibres. Despite adequate amounts of energy-rich phosphates electrochemical coupling does not occur, the energy present cannot be utilized. The other kind of insufficiency is the result of a true deficiency, be it of creatine phosphate, be it of oxygen. During the succeeding ten years Fleckenstein has advanced a concept which represents real progress: Below a certain level each deficiency of energy-rich phosphates, and particularly of ATP, produces:

(1) Loss of contractility and

(2) structural damage.

The deficiency of energy-rich phosphates may occur in two ways: In the first place there can be an inhibition of the synthesis of ATP by lack of oxygen, that means by ischemia attributable to the coronary arteries, or by an enzymatic inhibition of cellular respiration. On the other hand, an excessive increase in the utilization of ATP could produce similar results. Such an excessive increase in utilization could be caused by psychological or physical stress, *or* it could result from sympathetic overstimulation by the administration of Beta-adrenergic catecholamines. In the development of cardiac infarcts both factors could act together: Inadequate coronary perfusion *and* increased consumption of ATP by sympathico-mimetica ("stress"). If the degradation of ATP is not arrested at the level of ADP, AMP or adenosine, if it proceeds further towards useless products (inosine, xanthine), the threshold of regeneration, i.e. the recovery of the structure and function of the myocardial fibre, is exceeded when more than 60% of the adenine nucleotides have been destroyed. At the same time a very marked influx of calcium ions takes place. Catecholamines as such do not destroy the fibres. They only act via the excessive stimulation of the transmembranous influx of calcium ions. The pathological effect of calcium ions consists in an increased activation of the calcium-dependent myofibrillar ATP-ase. That way also a loss of ATP and creatine phosphate could take place.

The "epinephrine-myocarditis" has been known since 1922 (Doerr, 1971). It produces a fragmentation of the muscle fibres with a mobilization of the active mesenchymal interstitial cellular elements. This is not a myocarditis in the clinical sense, nor is it a myocardial infarct; it is the result of a chemical trauma!

The studies of Fleckenstein have elucidated the biotechnical aspects of the necrotization of muscle fibres mainly under experimental conditions. They allow, however, also an understanding of the development of necroses in the human myocardium. In a cardiac infarct the necrosis of the myocardial fibres in the affected territory is produced by the mechanisms described by Fleckenstein. But an infarct is more than a necrosis, and also different from a necrosis, or, to reverse the comparison: There are myocardial necroses which have nothing whatever to do with an infarct either from the phenomenological or from the causal-pathogenetic point of view. Nevertheless, nature uses the formal pathogenetic mechanisms studied by Fleckenstein (the consumption of substances supplying the energy needed for the maintenance of structure *and* of function, with an excessive influx of calcium ions). It is not easy for the unprepared mind to understand these connections, and I presume that precisely here lies the cause of misunderstandings.

It may well be so that, seen from the view-point of the pathological anatomist, "insufficiency due to deficiencies", i.e. myocardial damage caused by lack of coronary oxygen, affects in the *first* place the mitochondria, whereas "insufficiencies of utilization" affect first the transport apparatus of the tubuli transversales, and Selye's steroid cardiomyopathies the membranes and the sacroplasmic reticula. It is probable that in future we shall learn to attribute certain patterns of damage to well-defined conditions and associations which determine them.

In the current context, it is interesting to note that Baroldi (1975) also has tried to distinguish different forms of necroses—the necrosis of coagulation and colliquation on the one hand, and myocytolysis on the other.

Are there human myocardial necroses which are not determined by the circulation and which even the skilled prosector can distinguish only with difficulty from a myocardial infarct? From the time that the papers of Grunder-Culemann (1952, 1954) appeared, I have waited for such a case, but have encountered it only recently:

A man aged 51 years (SN 814/75) was admitted in poor condition to the University Clinic of Heidelberg with a diagnosis of cirrhosis of the liver. Because of a suspicion of a tumor of the head of the pancreas, an angiogram of the celiac vessels was done, followed by a persistent state of shock with kidney failure. During the two weeks of intensive treatment that followed, very irregular fluctuations of the serum ions developed and finally ventricular fibrilation supervened. The heart showed only moderate hypertrophy, but there were extensive greyish-white map-like areas of necrosis. These were predominantly situated in the left anterior wall of the ventricle and in the interventricular septum. The coronary arteries showed only a minor degree of intimal fibrosis; neither occlusion nor a significant degree of stenosis of even the smaller branches of the coronary vessels were found. The areas of necrosis were free of circulatory reactions in the surrounding tissue, there was no hyperaemic marginal zone and no significant zone of cell infiltration. What, however, could be immediately noted was *very* extensive calcification. This impregnation

by calcium affected exclusively the myocardial fibres. The interstitial connective tissue showed a pronounced edema, the coronary veins were markedly engorged. The necrotic areas were estimated to be 12–14 days old.

There was also present a beginning, only moderately well-developed, granular cirrhosis of the liver with fatty change and haemosiderosis. No tumor was found in the head of the pancrease, but there was present an induration by edema, as well as an obvious siderosis. Microscopically, several sections of the liver showed what appeared to be a recurring bout of hepatitis. Both suprarenal glands showed an acute regressive transformation of the cortex with a breakdown and collapse of the zona glomerulosa and fasciculata. Despite an intensive search no malignant tumor was found anywhere.

In the medical history of this patient a more than moderate degree of alcohol abuse cannot be dismissed. I interpreted the case as being an instance of "ESCN", that is a cardiomyopathy with necrosis and calcification caused by a convergence of the mechanisms invoked by Selye and by Fleckenstein: After shock had developed, steroid hormones on the one hand, catecholamines on the other were liberally administered. The transmembranous influx of calcium was the real, proximate cause producing myocardial death. The decreased coronary perfusion in shock and the administration of isoproterenol with its effects favouring the influx of calcium produced not only a consumption of the energy-rich phosphates. Where the necrosis was most pronounced, there could also be demonstrated histologically the most marked incrustation with, or incorporation of, calcium. It seemed as if the effects of cortisone and of isoproterenol had reinforced each other in furthering and potentiating the transport of calcium.

If, as a contribution to a *critical interpretation*, one in conclusion asks whether the case just outlined could be considered an example of a myocardial infarct, the answer must clearly be: No. If one, however, asks whether one was dealing with the consequence of a coronary insufficiency, the answer must be: Yes – but with a superimposed "metabolic necrosis". This means that under natural conditions in man such occurrences are not usually found, and that we were seeing here an example of iatrogenic pathology, an effect of treatment and unpremeditated side effects – an unexpected and unwanted experiment, so to speak.

The *focal point* of all the manifestations and consequences of the so-called coronary insufficiency is the *elective necrosis of the parenchyma.* To reproduce this clearly and cleanly in the animal experiment is not easy (Doerr, Höpker and Rossner, 1975). The elective necrosis of the parenchyma is the *logical* connecting link between the cardiac infarct and damage of the inner myocardial layers. The two, however, are certainly not synonymous. With Virchow we can say that the cardiac infarct is characterized by "speed and force" of development, and by the "nature of the danger". Anatomically the cardiac infarct represents an event of a disturbed circulation (note the hyperemic-haemorrhagic marginal zone), clinically it is characterized, amongst others, by shock.

The Whole is More than the Sum of Its Parts

A thousand necroses of myocardial fibres (in damage of the inner layers) never mature into an infarct. *But:* Once there is damage of the inner layers in the left ventricle, there may follow a disturbance of regulation with hypotonia, and this fall in blood pressure can (subsequently) produce a non-obturating infarct. A fresh infarct can then be superimposed upon older damage of the inner layers.

The myocardial infarct is not an additive phenomenon. In time and in space, it differs from damage to the inner myocardial layers. It occupies a

nosological position of its own. The functional mode of thinking of Ricker and Dietrich is – unintentionally – being again confirmed today: If one accepts that spasms can be important for the extent and the localization of an infarct ("angina"), at least as a secondary phenomenon (Hellstrom, 1975), the debate concerning the coronary arteries has reached a climax, and the concept of the dominant role of the coronaries for the development of infarcts has found decisive support. Pathology is not an abstract play with thoughts, but an empirical science. It is firmly rooted in natural science – as far as this is possible. That there are also additional forms and ways of knowledge is a matter of course for every pathologist.

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