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Editorial

Heterochronia and general pathology illustrated by the example of the human heart*, **

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The problem of heterochronia is an old one, probably dating back to Petrus Hispanus. He was the doctor who, better known as Pope John XXI., was supposed to have said: "*Tempus est causa corruptionis*" (Schipperges 1982). Obviously, Petrus Hispanus did not mean to contribute to pathogenesis in the sense of our contemporary pathological anatomy. But his basic thought was decisive and has remained important up to this day. My aim is to show the fruitfulness of this thought in relation to pathological anatomy, especially in respect to the human heart.

I shall consider the relationship between the phylogenetic development of various systems and the pattern of diseases which affect them and relate this to the apparent failure of some human systems to adapt, in the sense of evolving in a way which minimises the tendency to develop degenerative disease.

What kind of "*Corruptio*" is this? The expression goes back to Aristotle and was a legitimate term for centuries in the Greek schools of philosophy. It came down to us through the academy of Gondischapur in Asia (Schöffler 1979). This 'corruptio' was said to be necessary for man in order that his consciousness might become his self-consciousness (self-awareness). The corruptio was supposed to lead to the ability to recognise, – today, one would talk about achieving a "critical self-naturalness".

> Incidentally, Pope John XXI. died of a typical scholar's disease: He was battered to death when (in 1277) the library of his palace in Viterbo came tumbling down on him. His dying words were: "Quis perficiet libellum meum!" Who will look after my little book now? (Schipperges 1982).

I would like to refer to Cécile and Oskar Vogt, the brain research couple in Berlin-Buch and Neustadt (Black Forest) who – after prompting by Hermann Braus – reported on the pathological-anatomical principle of classify-

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** Dedicated to Professor Karl Rothschuh (Münster/Westfalia) – founder of the pathoclisis theory – on the occasion of his 75th birthday (8th July 1983)

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ing striatal motility disorders in the Golden Jubilee Publication to honour the anatomist Max Fürbringer (1919). The Vogts remind me of M. Wilson's work and Huntingon's chorea, which reveals the different types of pathological destruction of the priscostriatum and neostriatum. We think of Max Bielschowsky and his papers on the clarification of the diseases of the Corpus striatum, the historically approved term 'necrohamartosis' being one of the accidental fruits of his efforts (1918, 1920a and b, 1922). We also think of the concept of the so-called abiogenesis found by Schaffer and Miskolczy (1938) as a logical conclusion to the abiotrophy studies of Gower's (1902). My neuropathologist colleague here in Heidelberg, Professor Günter Ule, pointed out to me that two pathological manifestations are necessary for certain anthropomorphous functions in the process of ageing. One is *Pick's atrophy* with the disintegration of the phylogenetically young telencephalic windings which preferentially affect the peripolar parts of the temporal lobes as well as the basilar orbital cortex of the brain. Pick's atrophy occurs in the presenile period, the weight loss of the brain is astonishing. The other one is *cortical atrophy of the cerebellum* of a granular cell type. Here, the atrophic process affects the phylogenetically young parts of the cortex of the cerebellar hemisphere and of the cerebellar tonsils whereas the originally formed flocculi and the vermis remain intact. The reverse is also known: Phylogenetically old parts are affected, younger parts remain intact. Last but not least, I would like to mention the existing connections between various types of aftermath of Slow-Virus diseases, during the process of which a different pathoclisis is revealed in old ground as well as newly gained territory.

In any given context, the *determination of the time factor* plays a special part in that the constructive formation of an organ – the brain in our case – shows different stages of adaptation and maturation which thus represent the biotechnical precondition for very definite patterns of vulnerability. One *could* speak of a *heterochronia* as hypothesis for the topistic spreading of charactersitic disorders.

Robert Rössle, to whom I am grateful for stimulating my interest, explained in 1936 in Aschoff's textbook that all pathological alterations carry the hallmarks of heterochronia, heterotopia and heterometry: something happens at the wrong time and in the wrong place and in the wrong proportion, – *this* is the sign of pathological developments.

In Aristotle's corruptio – tempus est causa corruptionis – the time in the sense of physics is less important (sub specie pathologiae). Not even the philosophical side of the time factor is important at this stage – Kant regards the time as formal precondition for all being; the biological time in the sense of Gaston Backman (1943) of Sweden is closer to the mark. In 1980, Klaus Goerttler discussed the orthology and pathology of human development from the point of view of space and time with particular emphasis on growth gradients. *This* is, however, not how I would understand today's subject. I would like to say this: at the van Swieten Congress in Vienna in 1971, I tried to explain phylogenetic discrepancies in the supply of the coronary arteries to the human heart. I had in my contribution

to 'New Anthropology' by Gadamer and Vogler (1972) discussed the somatic fate of man as set out by Vincula in his history of evolution:

The development of the brain; the head size of the Nasciturus and sterility;
The increasing stress on the heart-circulation apparatus and physiological coronary insufficiency;
The placentation and immuno-critical threat to mother and fetus.

At the Congress of Pathology in Kiel in 1975 I elaborated on this and singled out the heterochronia as the cause of clearly defined discrepancies. Lastly I tried, together with W. Hofmann, to convey in a birthday paper for Hans Linzbach in 1980/81 (Göttingen) that, for reasons determined by evolutionary necessity, changes in the heart would occur if man would only grow old enough and why they would do this.

I think it would be best to proceed as follows:

1. I will take the development of the vertebrate heart as an example to demonstrate the meaning of hetrochronia and explain by which groups of disease it is followed.

2. I will draw similar observations for other organs.

3. Finally, I will try to make plausible from the law of evolution why our opinion about the pathogenesis of heterochronia has something to offer.

Back in 1937, when I asked my teacher Alexander Schmincke – then Professor of pathological anatomy at Graz, Tübingen and Heidelberg – for a theme for my thesis, he suggested that I should persue Alexander Spitzer's theory of heart development and heart deformation. At Julius Tandler's institute in Vienna, Spitzer had worked on "Causes and mechanisms of the dichotomy of the vertebrate heart" ever since 1919. Spitzer was determined to explain through phylogenesis certain courses of events such as torsion (twisting) at the arterial and countertorsion at the venous end of the heart.

He achieved two aims: The recognition of the alternating and connective switching of the arteries of the lung and the body *and* a certain parallel between the organisation of the external respiratory movement and the so-called torsion which is indispensable during the switching process. Spitzer's fascinating idea sparked off a highly stimulating debate about the formal development of congenital heart defects. Obviously, Spitzer did not mean to say that recent heart defects are atavisms (relapses) i.e. truthful copies of, say, a reptile heart. However, the example of the technical material movement within an indefinite time scale and in connection with the clear-cut evidence did allow a *natural-historical interpretation.* In other words: the defect of the external respiratory movement could be connected to the lack of torsion at the arterial end of the heart. I have repeatedly reported on the details of this (1970, 1980). In the decades between 1940 and 1970, Spitzer's theory attracted more criticism than approval. Pernkopf and Wirtinger (1933) had pointed out some of his errors which occurred when Spitzer was working on comparative-anatomical data. Therefore, the ontogenetical viewpoint was favoured. This stand, although fully justified, clouds the view for higher connections if the aim is to establish the formal origin

of certain defects. Adolf Portmann in Basle pointed out that if one working method lacks the approved techniques of an otherwise tried method – as happens in a morphological comparison with the systematic order of pathological phenomena in the course of evolutionary changes – it must not deter us from the recognition that in such a context certain constellations in the findings represent a link with reality (Portmann 1970).

When dissecting a New Year's Eve carp (Cyprinus carpio), one comes across a longitudinally oriented heart comprising some compartments in the cranial and some in the ventral area. It shows a caudocranially ascending, slow (idle) venoarterial contraction. Primarily, the heart is built metamerally, whilst an antimeral segmentation is phylogenetically achieved only very much later. There is a tendency towards progressive metamerisation.

Blood transport as well as type and location of the oxygen intake form a close relationship. Klaus Goerttler has pointed this out repeatedly (1958, 1963). As the heart as a muscular organ had to find a new shape – it changed from a tube-shaped organ to a compressed bow – a strange event occurred: the blood stream threads started to tie each other off in a spiral. This resulted in a contorted run of the two circulations, i.e. the organisation of the alternating and the parallel switching of the pulmonary and systemic blood stream.

In the context of the history of our universe, these events occurred in the Devonian age when the land masses were over-run by amphibias and reptiles. The blood circulation speed on the one hand and the utilisation of the blood gases on the other hand had to increase. Relevant to our discussion are the transitionary species between reptiles and vertebrates. These are called theriodont and lived in the cretacious period. From then on, an antimery, that is to say a proper dichotomy of the heart, should have existed. The hearts were now working rhythmically, having developed longitudinal muscle bridges under the endocardium and thereby the first outline of the specific muscle texture.

The Devonian was the age of massive plant development. There must have existed a divergent evolutionary trend. Birds appeared as refined reptiles. Archaeopteryx is the oldest bird known and an intermediate form between reptiles and birds. Transitionary stages between birds and vertebrates, however, have never been found.

Our heart has *four special features*:

1. It is organised in a metameral and antimeral way;
2. It serves the large and the small circulation simultaneously;
3. The large and small circulations are being switched in a parallel and serial fashion; they serve each other in the sense of a quantitative exchange;
4. The veno-arterial contractions are controlled by acceleration and deceleration i.e. a rhythm.

In the 4th to 7th week of embryonic development, an event takes place that probably reaches back to the Devonian and Cretacious period. The disposition of the heart chambers consists of a metameric form which, very much later, the inlet stream of the cardiologists emerges, and it consists of a second, linking metamere with the outlet stream. Both compartments are shunted into and against each other in a complex way and thus together

form a complicated unit. The right chamber is the initial element, called the paleomyocardium; the left chamber is a grotesquely dislodged thing, an creative element, called the neomyocardium. The inlet streams of both chambers – right totally, left partially – go back to the proximal chamber metamere; the outlet streams of both chambers – left totally, right partially – go back to the distal metamere. The wall of the left chamber shows signs of heterochronia. By this I understand that phylogenetically old and young organ structures had to join in a functional togetherness without the maturating stages of the building elements having been chronologically adapted.

This fact contributes to the pathogenesis of *three groups of diseases*:

1. Right-Left problems of defect patterns on the completed human heart.
2. Favoured topographical ligature (tie) of myocardial infarction.
3. Rhythmical interferences through lateral connections and (so-called) coelothelioma inclusions.

The pathoclisis of the ventricle walls has been comprehensively studied by Jansen (1962). It is of special interest that the relation between the surface of the right ventricle capillaries and the surface of the muscle fibres seems to have shifted just here by one third in favour of the capillaries when compared with the appropriate measurements of the left ventricle.

This implies that the right ventricle wall is a third better off than the left with regard to oxygen supply.

This also means that toxic matters carried to the heart muscle by the bloodstream are diffused by one third more via the right coronary capillaries than the left ones. So, what is lucky with respect to the oxygen supply is not at all advantageous with respect to pressure applied via the blood vessels. This statement has been proved many times.

The differences in texture between right and left ventricle wall are well known to the expert. The muscle fibres on the right are staggered, on the left they are arranged in a packeted fashion. These peculiarities have nothing to do with increased pressure or volume, for contracted defects such as pulmonary sclerosis, high pressure syndrome, right ventricle *or* insufficiency of the aorta, volume increases of the left ventricle do not change the basic structure. The pattern of development followed for millions of years remains the same! Contracted defects may show up adaptative secondary features, but they do not change the original structures.

The coronary arteries have their own history

The simplest form of blood supply to the ventricle walls takes place through sinusoids (recesses) from the ventricle lumen. In certain types of amphibians (tail batrachia), one arteria coronaria is already existent. Reptiles have special features which I cannot go into at this stage. Some, especially tortoises, and of these the alligator tortoise, possess an apex cordis band. Here, one can find an additional hypobranchial artery as well as more or less well established orthodox coronary arteries. Birds, vertebrates, even man, have apex cordis bands with blood vessels. Primates are vaguely related to the tupaia, a very agile type of squirrel in East Asia which cannot be easily

bred. The coronary arteries emerge from an intramyocardial shrub-like pattern of vessels. In the context of the systematic history of mankind, the human coronary conditions are linked to those of the insectivores. The human heart has the primitive outlines of a right coronary type. The human coronary dextra represents a unified closed vessel; the left coronary artery in humans consists of several, at least three, parts. In this context, I am not talking about the coronary right or left supply type used in clinical cardiology, I want to stress the comparative anatomical classification. The recent coronaria sinistra of man consists of disparate line sections.

Initially, the human fetus carries a dorsal mesocardium for about a fortnight. From this a vascular bridge leads between the front arm to the back of the heart along the level of the atrivoentricular border zone. This vessel bridge is retained as Haas' artery. It represents the relic of a 4th coronary artery.

We don't know why we only possess two instead of four arterial supply lines to the heart and why the apex cordis band (with the third coronary) and the dorsal mesocardium (with the fourth coronary) have disappeared. Where the Haas artery penetrates the dorsal ventricle wall, some remnants of these sometimes remain. These develop into divided mesothelioma-like tumours called *coelotheliomas*. These can affect the action of the heart muscle because they are situated right next to the atrioventricular knot.

The vast majority of coronary infarctions occur in those places where the inlets of those accidental arteries were situated. They occur therefore either in a ventroapical or dorsobasal position. I want to make this very clear.

It is known that our heart possesses certain anastomotic fields. It is not really plausible to accept that infarctions chose to occur in the inlet places of these long-lost supply lines. But there is no doubt about these facts. Therefore, it has to be assumed that the extravascular resistance towards coronary perfusion, the topography of the vegetative nerve endings or the neurohormonal harmony, are different from those situated in the neighbourhood of historically grown, old and evenly distributed arteriolomyocardial synergides. The functionality of the terminal blood stream line of the heart muscle therefore, has not yet reached that stage of reliability in those places which probably were arteriolised in their own fashion, that is, they needed to cut out life-threatening attacks in the event of a crisis. To possess anastomoses and to make them work are therefore two different things.

I now come to the *third group of large potential impairments*. It is well known that our heart is controlled by a "système de commande du coeur". There is a well characterised conduction system which represents the shortest geometrical muscular connection between venous inlet and arterial outlet. Wilhelm His jun. in Leipzig found in 1893 a bundle of muscles which was named after him and which constitutes the bridge fibres between antechambers and ventricles[1]. In 1905, Tawara discovered the atrio-ventricular knot while working for Aschoff in Marburg. In 1906/1907 Keith, Flack

1 „Zur Geschichte der Entdeckung des Reizleitungssystemes". Doerr W. (1963). In: Schiebler TH, Doerr W

and Ivy Mackenzie found the sinus knot at the upper vena cava funnel, following a suggestion by Wenckebach. Walter Koch, Professor of Pathology in Berlin-Charlottenburg, went into more details on this subject.

This was the time of the first topological investigations along the lines of heart block studies. There is a famous incident: When Dr. James Mackenzie in Burnley (England) sent the heart of a man who had died of recurring bypass defects to Sir Arthur Keith, asking him to investigate the newly discovered knot (by Aschoff and Tawara), Sir Arthur confessed that he did not have a clue. After writing back to Aschoff, however, he found what he was looking for. I therefore want to report and stress that Keith – a brilliant anatomist, anthropologist and comparative histologist – asked the vital question: one would have to investigate why it is that such a primitive muscle came to lie in phylogenetically such a young place. Keith's statement, wrapped into a question, has value for eternity. He saw what the discoverer, Aschoff, did not contemplate: that namely the specific muscle represents the prototype of the transporting priscomyocardium, situated in a phylogenetically young place and contracted through the basal septation of the vestibulum during the reptile state. This is Heterochronia.

The specific muscle texture is only present in the old heart area, mainly in the right ventricle. The right coronary artery, that is to say the older one, supplies all crucial positions, namely the centres of conduction and the His bundle. Atrioventricular parallel connections are only thinkable within the priscomyocardium, that is to say, at the dorsal septum areas. The right part of the system is the evenly built, historical one; the left one was acquired later and is more unstable and likely to be affected by various impairments.

The pace-maker cell of the conduction centres is the historical example of a heart muscle cell that works automatically as a transmitter throughout the entire vertebrate species.

So far, so good. There are three cardiac groups of diseases the roots of which lie in a phylogenetical area.

Side discrepancies in defects and interferences in the ventricle walls.
Places of predilection of myocardial infarctions.
Definite rhythmical defects inclusive of mors subita cardiaca.

All this can only be understood if one knows what heterochronia means!

Does anything like this happen in other organs?

We have mentioned the brain and the heart; endocrine glands and the neuroendocranial system show comparable irregularities such as progonomas or progonoblastomas. Endocrine organs will occur in areas where this does not happen in normal ontogenesis. Even in the anatomical field of the body and the mammary line find peculiarities: in the area of the human face fissural basaliomas, in area of the mammarial line accessoric mammary glands, even in the groin. One could call this "atavistic reminiscences" which only paraphrases a process that in the formal morphogenesis was

inadequately explained. Heterochronia exists of course also in other organs, a fact that must not be underestimated in the roll of a so-called organ disposition for contracting various pathic phenomenons.

Heterochronia, as a principle of pathogenesis in the sense of a higher precondition for the development of some groups of interferences, gathers probability in the relation to the evolution of man. The idea of evolution has acted, ever since Darwin, in a binding and somehow classifying fashion. Chance and necessity play a decisive part in the process. Chance and rule are the elements of the game. In biology, the occurrence of irreversible processes has a special meaning. Structures are developed which are a far cry from the balance in the sense of physical chemistry. Thermodynamic balances are geared towards dying and death, stationary non-balance systems towards life, even immortality. Evolution means the occurrence of complicated (intricate) connections. Irreversibility is a crucial feature self-organisation. The course of evolution probably runs through 3,500 million years. The evolutionary speed is comparatively fast. It causes considerable vulnerability in the inheritance, so we think. Man is neither an aberration of nature nor does nature look after his survival. Here starts what we might call philosophical anthropology.

Let me pinpoint the following provisional result: heterochronia represents an "impartial" principle which provides the researcher with unlimited food for thought. One would like to ask the question why the motor of our life, namely our heart, was constructed by hook and by crook, sacrificing two additional arterial supply lines, just in order to bring about a massed muscle knot divided into ventricles and equipped with an astonishing pushing force? Had we not had this artistically designed thing which musters about 40 million contractions per year ever since the cretacious period, we would not have developed into a "brainy animal with something else attached", as is mentioned in some literature.

It is just as if the breakthrough from a vegetative existence (where retaining the primitive cardiovascular apparatus would have been sufficient) to an active and agile and eventually intellectual life was compelled to occur long before a new and sufficient safety mechanism was estabished. The phylogeny of man is particularly attractive to the pathologist because we are forced into thinking spheres which reach far beyond our subject into higher connections.

I believe that the text in the first book of Moses (chapter 1, verse 27) – where the possibility to see the greatness of our creator is expressly stated – could be brought up to date through the complexity of the questions here presented.

Summary. 1. Heterochronia, heterotopia and heterometria are important elements of the pathogenic process.

2. Heterochronia has its historical roots in the philosophy of Aristotle.

3. As the organs of living creatures and especially man have developed, the process has been one of fitting together a variety of evolutionary bricks.

4. Each complex organ shows evidence of a gradual control of its cellular structure. Parts of organs observed at different stages of man's development all appear to retain certain heterologous (identical) organisational features.

5. Thus, the different pathoclisis is explained.

6. Classical Neuropathology has made headway in this field. Its methodical procedure was adopted – mutatis mutandis – by General Pathology. The inherent structural weaknesses within the organisation of the human brain are, in their organic type of differentiation, also present in the muscular heart.

7. The right ventricle has developed mainly from the myoepicardium of the proampulla; the left ventricle has its origin in the metaampulla. The right ventricle consists mainly of priscomyocardium, the left one of neomyocardium.

8. This is the basis on which are founded the main characteristics of the muscular structures, the arrangement of the coronary arteries and the organisation of the conduction system.

9. A. Keith had already discovered in 1906 that the elements of specific muscle texture contain old structures. We believe that the pacemaker cell represents the historical paradigm of the working muscle cell of the heart (the transporter).

10. Atrioventricular collateral connections (anastomoses) are only found within the priscomyocardium, the arteria coronaria dextra being the original. The coronaria sinistra was evolved later.

From the summary of facts originating from the heterochronia of heart development we can draw conclusions about the development of the major heart diseases such as:

Those which are dependent on interference with the ventricle walls following oxygen deprivation and the resulting toxic stress;

Those which are characterised by infarction of the myocardium which occur in areas which have a predilection for such reaction and which can be set out in a predetermined topology;

Those characterised by rhythmic interferences of the heart caused by atrioventricular collateral connections;

as a result of an anthropological pathomorphology.

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