Virchows Arch. A Path. Anat. and Histol. 389, 225–240 (1980)

Virchows Archiv A

The Concept of Homology in Quantitative Organelle Pathology

Application of Symbolic Logic to Glycogenosis Type I in the Liver

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Summary. The process of quantification has led pathology into an objective and abstract direction to which it is unaccustomed. The introduction of the concept of homology in pathology by Doerr has proven to be very fruitful, since it has helped to clarify otherwise poorly understood relationships. As shown in the foregoing paper, the succes of the homology concept applies also to quantitative organelle pathology. Homologies have demonstrated relationships within the ergastoplasmic – mitochondrial – peroxisomal system which are apparent only with the help of symbolic logic. These homologies permit inferences, shown here with the example of glycogenosis type I, regarding the adaptive potential of the cell and the degree of cellular damage. In addition, these homologies, which are described in terms of formal logic, may serve as a model for human pathologic anatomy.

Key words: Homology – Morphometry – Symbolic logic – Organelle pathology – Glycogenosis.

Introduction

A major role of the pathologist is the classification of morphologic and functional changes in organs and cells in various disease entities. The important step in formulating a diagnosis may proceed along two different paths: (a) a simple list of features, or (b) pattern analysis. When a diagnosis is made on the basis of a list of features, the presence of each possible characteristic in a diseased organ is looked for. This process is exact but time-consuming, and is used

Supported by Grant Ri 271/5 from the Deutsche Forschungsgemeinschaft, West Germany. Dr. Moore is a Research Fellow of the American Heart Association Maryland Affiliate, Inc., USA

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0340-1227/80/0389/0225/$03.20

only for particularly difficult diagnoses. When a diagnosis is made on the basis of pattern analysis, the individual tissue changes characteristic for a particular disease are assembled as a pattern, and the presence of this *pattern* is then looked for. This process is very rapid, but often leads to incomplete or incorrect diagnoses. Diagnoses made on the basis of descriptive morphology are extremely subjective, since they rely upon the following thought process : concept → judgment → conclusion. Before one forms a judgment, which sometimes comes to a halt at the level of a provisional diagnosis, it is desirable to have a "preconcept" for the material, that is, a concept "in the process of formation" (Bloch 1975). In this manner the subjective impression of the diagnostician is guided in an objective direction, using measurements, without limitations imposed by a particular school of thought. This upgrading of observations, in the form of a "preconcept" for the material, may then serve as the basis for a concept (= result of measurement, criterion) using a process of weighted judgment (= analysis). Only then is it appropriate to form a conclusion (= diagnosis).

Quantitative pathology may assist the process of upgrading observations as "preconcepts" by making three essential types of judgments:

(a) logical quality with the formation of yes-no decisions,

(b) logical quantity with the abstraction of superfluous statements,

(c) logical modality with the introduction of the "possible".

Logical modality offers the pathologist the opportunity of incorporating the property of "becoming" (as opposed to "being") as part of his diagnoses. Logical modality has been introduced into quantitative pathology as symbolic logic supplemented by "certainty levels", or subjective grades of certainty (Moore et al. 1979). This modality approach is exemplified in cytopathology in the form of diagnoses such as "suspicious for tumor" versus "positive for tumor" (Moore et al. 1980).

In his paper entitled "Rule of Homology and Morbid Anatomy," Doerr (1979) illustrates the homology concepts using morphologic sequences with topographic, histologic, and histogenetic criteria. He shows that homology is important for revealing otherwise unintelligible relationships. Since this manner of thinking has opened up new areas of contact between philosophy and pathology, it has given rise to special difficulties. These difficulties may be resolved in part by the introduction of mathematical logic.

In the foregoing paper, the concept of homology is applied to the problem of concept formation in quantitative organelle pathology (Riede et al. 1980a, b, d; Moore et al. 1977), and is tested for validity using symbolic logic. It shall be demonstrated that, as in pathology, as soon as measurements are introduced to objectify observations, relationships appear which elevate the process beyond the merely subjective judgment.

Materials and Methods

1. Materials

Morphometric data from our own laboratory and from the literature were employed for the analysis of reaction patterns which appear in different phases of acute or sublethal cellular injury. Data

from a total of 115 different experiments were analyzed (Riede et al. 1980a). As an example of the homology concept, the morphometric data and the results of symbolic logic analysis from two patients with glycogenosis type I were selected. The clinical data for these patients have been published elsewhere (Spycher and Gitzelmann 1971 Riede et al. 1980c).

As the example of juvenile glycogenosis type I, we employed data from a 3-year-old boy with biochemically and clinically confirmed glucose-6-phosphatase deficiency, who had died six months following liver biopsy (Riede et al. 1980c). The case of adult glycogenosis type I was a 22-year-old female patient with biochemically and clinically confirmed glucose-6-phosphatase deficiency. At the age of 19 this patient was found to have a hepatocellular adenoma, which was removed surgically three years later (Spycher and Gitzelmann 1971).

The liver biopsy from a 3-year-old boy with biochemically and clinically normal metabolism and normal liver, who had been operated upon for repair of an umbilical hernia, served as the juvenile control (Riede et al. 1980c). The morphometric values of liver biopsies from 25-year-old healthy volunteers were used as adult controls (Rohr et al. 1976).

Liver tissue was fixed in cacodylate-buffered OsO_4. Embedding with Epon. Uranyl-lead contrasting of ultra-thin sections. Ultrastructural-morphometric analysis of hepatocytes by the method of Weibel et al. (1969), modified (Rohr and Riede, 1973; Rohr et al. 1976).

2. *Symbolic Logic*

Symbolic logic is a mathematical method in which both quantitative and descriptive statements may be placed in formal relationship to one another (Quine 1950; Carnap 1958). In principle any data or conceptual information which can be expressed in a natural language (such as English) can be translated into symbolic logic.

The fundamental components of symbolic logic are *unit statements* and *operators*. A unit statement is a simple assertion written in a natural language. *Operators* are used either to qualify a statement or to show the relationship of one statement to another statement. Commonly used operators include: negation (−), and (&), inclusive-or (|), implication (>), backimplication (<), and equivalence (=). (Symbols chosen for their availability on most computers). *Compound statements* are constructed from one or more unit statements, connected by operators. Thus if A is a statement, then $-A$ symbolizes the (compound) statement with the opposite truth value. That is, $-A$ is true if and only if A is false. Likewise, if A,B are statements, then statement A&B is true if and only if both A *and* B are true; statement $A|B$ is true if and only if either of A *or* B are true (or both); statement $A>B$ is true if and only if whenever A is true, B is true; statement $A<B$ is true if and only if $B>A$ is true; and statement $A=B$ is true if and only if *both* $A>B$ and $B<A$ are true.

Solution of a system of symbolic logic involves transformation into a standard form and then calculation of all logical conclusions. The transformation into standard form is a modified Gentzen reduction, described elsewhere (Quine 1950; Anderson and Johnstone 1962; Snyder 1971; Moore et al. 1977, 1979). The initial symbolic logic expression is negated. Every appearance of A>B is converted into $-A|B$; every appearance of $A<B$ is converted into A|−B; and every appearance of $A=B$ is converted into $(-A|B)$ & $(A|-B)$. Every appearance of $A|B$ is separated into two expressions, A and B (Separation Rule). Every appearance of $--A$ is converted into A (Double Negation Rule). Every appearance of $-(A \& B)$ is converted into $-A|-B$; and every appearance of $-(A|B)$ is converted into $-A \& -B$ (De Morgan Rule). Every appearance of $(A|B) \& C$ is converted into $(A \& C)|(B \& C)$ (Distributive Rule). The Separation, Double Negation, DeMorgan, and Distributive Rules are applied repeatedly to exhaustion. Each such string of statements (connected exclusively by &) are the members of a single set, called a *nullity* (Quine 1948).

A nullity (Moore et al. 1977, 1980) is a set of unit statements of their negations which, taken in combination, are *false*. The nullity $\{A\}$ expresses the condition, "it is false that A"; the nullity $\{-A\}$, on the other hand, expresses the condition, "it is false that not A", in other words, "it is true that A". The nullity $\{A, B\}$ expresses the condition, "it is false that *both* A and B are true," or "either A is false or B is false (or both)", etc. The *empty nullity*, $\{\}$ or $\emptyset$, signals a contradiction in the system. The final step in the calculation involves exhaustive application of *null addition*, denoted $\oplus$, an arithmetic step akin to ordinary addition. This is the *Quine-McCluskey algorithm* for simplifying truth functions (Quine 1952, 1955; McCluskey 1956; Moore et al. 1977;

Moore et al. 1979). Two nullities say $\{A, B, C\}$ and $\{-C, D, E\}$, are subject to this operation if and only if there is exactly one element, called the *sign reversal element* (here, element C), which is positive in one nullity and negative in the other. The *null sum* is defined as the set containing the members of both sets *except* the sign reversal elements, i.e., $\{A, B, C\} \oplus \{-C, D, E\} = \{A, B, D, E\}$. Null addition is performed to exhaustion on all allowable pairs of nullities in the system. This calculation has been shown by rigorous mathematical proof to find all and only the valid nullities in the system.

3. Quantitative Organelle Pathology

We employ a logical model of organelle pathology in terms of the general pathology of growth disorders (Moore et al. 1977; Riede et al. 1980a, b, d). This model employs a subdivision of the hepatocyte (H) into seven organelles: nucleus (N), mitochondria (M), peroxisomes (P), lysosomes (L), rough endoplasmic reticulum (R), smooth endoplasmic reticulum (S), and mitochondrial cristae (C). These organelles are either particulate organelles (N, M, P, L) or tubulocisternal organelles (R, S, C). Particulate organelles, tubulocisternal organelles, and the hepatocyte as a whole, are collectively termed *compartments*.

Measurements. Compartments H, N, M, P, L are characterized in terms of *volume density*, $\bar{V}$, *numerical density*, $\bar{Z}$, *surface density*, $\bar{F}$, and *volume to number ratio*, Q. Compartments R, S, C are characterized in terms of *volume density*, $\bar{V}$, *surface density* of the organelle membranes, $\bar{F}$, and *volume to surface ratio*, Q. Each morphometric measurement is quantified as significantly increased (H, "high"), normal (N), or significantly decreased (L, "low"), using 95% Student confidence limits. Each measurement is written in a three-letter shorthand, xyz, where x is the compartment (M, P, L, etc.), y is the quantity being measured ($\bar{V}, \bar{Z}, \bar{F}$, etc.), and z is the amount of that quantity (H, N, L). For example MVH denotes "volume density of mitochondria increased (high)".

Morphometric parameters $\bar{V}$, $\bar{Z}$, and $\bar{F}$, for the nucleus (N) and hepatocyte (H) have unit volume of liver tissue (1 cm^3) as the reference system, and correspond to the standard morphometric symbols V_{VN}, N_{VN}, S_{VN}, and V_{VH}, N_{VH}, S_{VH}, respectively. Morphometric parameters $\bar{V}$, $\bar{Z}$, and $\bar{F}$, for all cytoplasmic organelles (R, S, M, C, P, L) have *volume density* of cytoplasm (V_{VC}) as the reference system, i.e., volume fraction of hepatocellular cytoplasm per unit volume liver tissue (cm^3), and correspond to the standard morphometric symbols V_{VM}/V_{VC}, N_{VM}/V_{VC}, S_{VM}/V_{VC}, S_{VMO}/V_{VC} (here given for mitochondria). Particulate organelles (N, M, P, L) and the hepatocyte (H) are characterized additionally in terms of volume to number ratio, Q, volume density divided by numerical density of particulate organelles, and corresponds to the standard morphometric symbol, V_{VM}/N_{VM} (here for mitochondria). This ratio allows estimation of the mean single volume of particulate organelles. Tubulocisternal organelles (R, S, C) are characterized in terms of *volume to surface ratio*, Q, or volume density divided by surface density of a tubulocisternal organelle, and corresponds to the standard morphometric symbol V_{VSER}/S_{VSER} (here for the smooth endoplasmic reticulum). This ratio allows estimation of the mean width of the endoplasmic reticulum cisternae or the space between cristal membranes.

A system of nine pathologic and five morphologic diagnoses was employed for each organelle. Pathologic diagnoses were: normal (N), proliferation (P), ageneration (E), hypertrophy (T), atrophy (A), hyperplasia (R), hypoplasia (O), dysplasia (D), and dystrophy (Y). Morphologic diagnosis were: unchanged single volume (U), microorganelle (C), small organelle (S), megaorganelle (M), and giant organelle (G).

3.1. Morphologic Diagnosis. The *unchanged state* (U) shows organelles with a normal single volume. The *small organelle state* (S) shows organelles with moderately decreased single volume in which either the organelles volume density is not low or the numerical density of the organelle is not high. The *microorganelle state* (C) shows organelles with such a decreased single volume that both the volume density is low and the numerical density is high. The *megaorganelle state* (M) shows organelles with a moderately increased single volume, in which either the organelle volume density is not high or the numerical density is not low. The *giant organelle state* (G) shows organelles

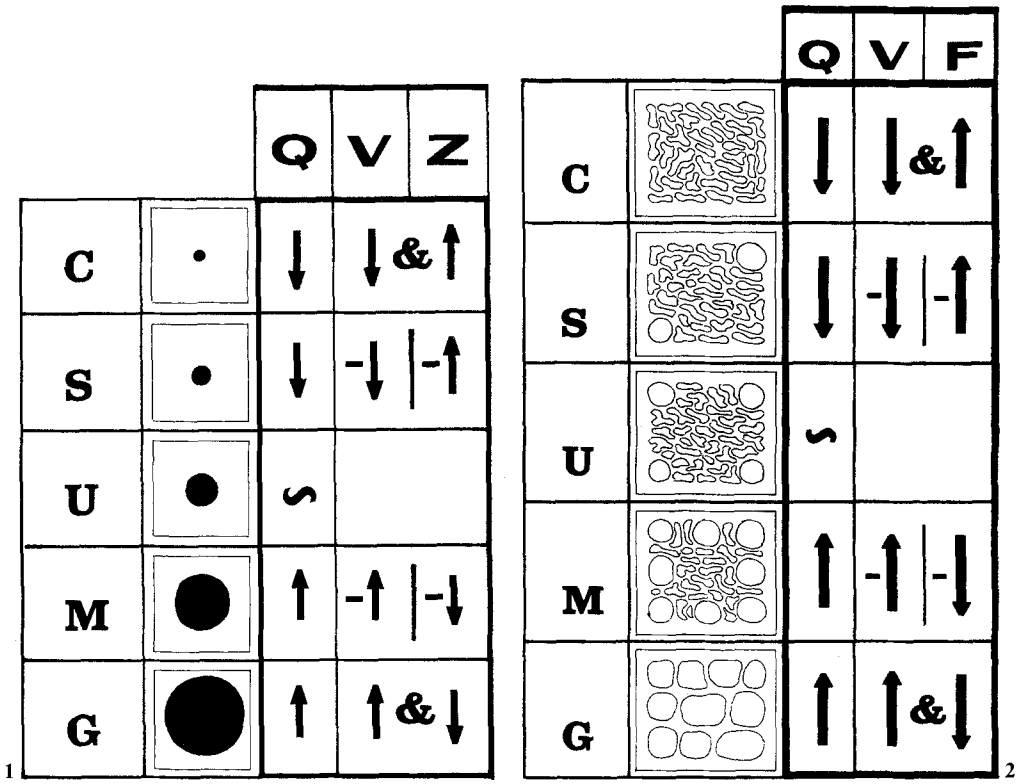

Fig. 1. Morphologic states of particulate organelles (e.g., mitochondria) in a quantitative organelle pathology. Five morphologic states are represented diagramatically: *U*, unchanged morphologic state; *C*, microorganelles; *S*, small organelles; *M*, megaorganelles; *G*, giant organelles. *Q*, volume density to numerical density ratio (quotient); *V*, volume density; *Z*, numerical density

Fig. 2. Morphologic states of tubulocisternal organelles (e.g., smooth endoplasmic reticulum) in quantitative organelle pathology. *U*, unchanged organelles; *C*, microorganelles; *S*, small organelles; *M*, megaorganelles; *G*, giant organelles. *Q*, volume to surface ratio (quotient); *V*, volume density; *F*, surface density of organelle membranes

with such an increased single volume that both the organelle volume density is high and the numerical density is low (Figs. 1, 2).

3.2. Pathologic Diagnosis. Proliferation (*P*) is defined either as an increase in numerical density without change in volume density in particulate organelles or as an increase in surface density without volumetric change in tubulocisternal organelles.

Ageneration (*E*) is the opposite of proliferation, defined as a numerical reduction in particulate organelles or as a reduction in surface density in tubulocisternal organelles, without simultaneous volumetric changes.

Hypertrophy (*T*) is defined as volumetric increase without change in particulate organelle number or in surface density of tubulocisternal organelles.

Atrophy (*A*) is the opposite of hypertrophy, defined as volumetric decrease in organelles, without change in numerical density of particulate organelles or in surface density of tubulocisternal organelles.

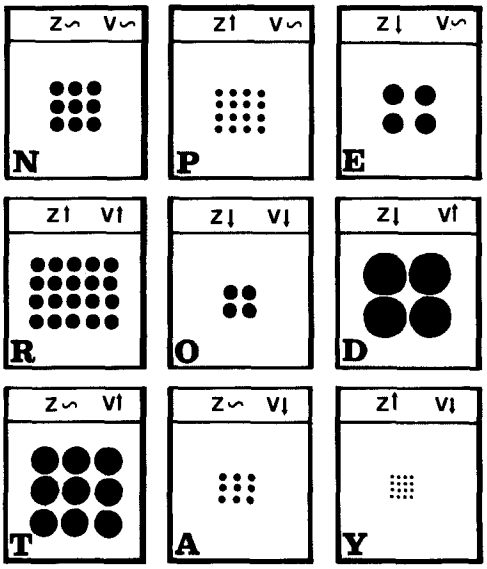

Fig. 3. Pathologic states of particulate organelles (e.g., mitochondria) in quantitative organelle pathology. Nine pathologic states are represented diagramatically. *N*, normal state; *P*, proliferation; *E*, ageneration; *R*, hyperplasia; *O*, hypoplasia; *D*, dysplasia; *T*, hypertrophy; *A*, atrophy; *Y*, dystrophy. *Z*, numerical density; *V*, volume density, ~ unchanged morphometric values, ↑ significantly increased morphometric values, ↓ significantly decreased morphometric values

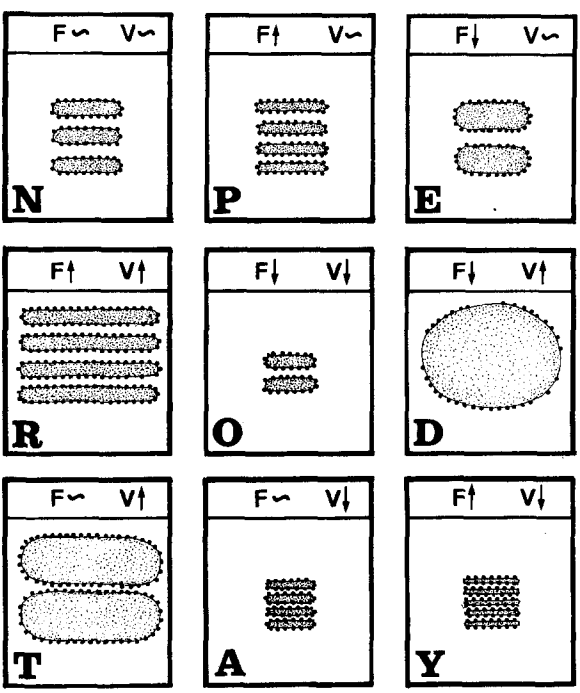

Fig. 4. Pathologic states of tubulocisternal organelles (e.g., rough endoplasmic reticulum) in quantitative organelle pathology. Nine pathologic states are represented diagramatically. *N*, normal state; *P*, proliferation; *E*, ageneration; *R*, hyperplasia; *O*, hypoplasia; *D*, dysplasia; *T*, hypertrophy; *A*, atrophy; *Y*, dystrophy. *F*, surface density of organelle membranes. *V*, volume density. ~ Unchanged morphometric values, ↑ significantly increased morphometric values, ↓ significantly decreased morphometric values

Hyperplasia (*R*) is defined as a numerical and volume increase in particulate organelles or as volume and surface density increase in tubulocisternal organelles.

Hypoplasia (*O*) is the opposite of hyperplasia, defined as a numerical and volumetric decrease in particulate organelles or as a volume and surface density decrease in tubulocisternal organelles.

Dysplasia (*D*) corresponds to a numerical reduction with simultaneous volumetric increase in particulate organelles, or to a surface density reduction with simultaneous volumetric increase in tubulocisternal organelles.

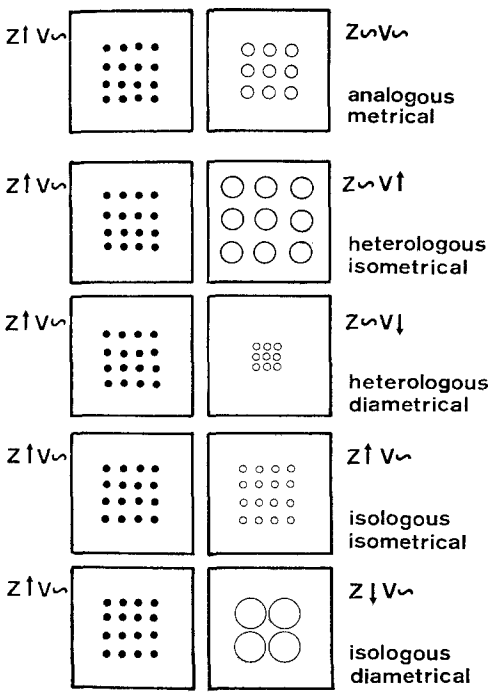

Fig. 5. Graphic representation of all homology types which appear in quantitative organelle pathology. Example: mitochondria = black circles; peroxisomes = white circles

Dystrophy (*Y*) is the opposite of dysplasia, defined as numerical increase and volume decrease in particulate organelles, or as surface density increase and volumetric decrease in tubulocisternal organelles (Figs. 3, 4).

Each possible pathologic and morphologic diagnosis was written out as a two-letter shorthand, with the first letter denoting the compartment (*R, M, P,* etc.) and the second letter denoting the pathologic (*N, P, E,* etc.) or morphologic (*U, C, S, M, G*) diagnosis. For example, *MR* denotes "mitochondria hyperplastic" and *MC* denotes "micromitochondria" (Table 4).

Results

1. Homology Types in Quantitative Organelle Pathology

The morphologic diagnoses do not produce a simple morphologic description of organelle change, but rather represent essentially a mean morphology of the given organelle x with respect to the reference organ. For particulate organelles (nucleus, mitochondria, peroxisomes, lysosomes), this involves an assignment into five different size classes. For tubulocisternal organelles (RER, SER, mitochondrial cristae), this involves graded levels of vesiculation, vacuolization, or collapse of the given compartment y. Likewise the pathologic diagnoses do not describe individual changes within organelle x, but rather give the pathologic growth disturbance of the cellular organelle with respect to the organ as a whole in terms of concepts of general pathology (e.g., atrophy). The unification of pathologic and morphologic diagnoses both for particulate and for tubulocisternal organelles allows one, first of all, to compare pathologic diagnoses in organelles of differing configurations with one another (Table 4). This same assumption (i.e., ability to compare changes in different organelles) underlies the determination of different homology types of morphometric changes.

If one considers the manner in which individual compartments of a cell within an organ (such as the hepatocyte) may be altered morphometrically, one recognizes two major homology groups:

a) changes of the same morphometric parameter in both compartments, x and y, being compared.

b) comparable or contrasting change in the morphometric parameters of the two compartments, x and y, being compared.

If morphometric parameter p in organelle x and morphometric parameter p in organelle y are altered, then this is called an *isologous* homology type. On the other hand, if morphometric parameter p in organelle x and morphometric parameter q in organelle y are altered, then this is called a *heterologous* homology type (Fig. 5). If morphometric parameter p in organelle x is altered in the same direction as morphometric parameter p in organelle y, then this is an *isologous-isometric homology*. But if this morphometric parameter p is altered in opposite directions, then this is an *isologous-diametric homology*. It is possible, however, for morphometric parameter p in organelle x to be altered in the same manner as morphometric parameter q in organelle y, which is called a *heterologous-isometric homology*. If the morphometric parameters p and q are altered in opposite directions for organelles x and y, then this is called *heterologous-diametric homology* (Fig. 5). Finally, there are also cases in which organelle x does not exhibit any morphometrically determinable changes, whereas organelle y is quantitatively altered. This is called *analogous-metric homology* (Fig. 5).

(a) Isologous-Isometric Homology Type. The following combinations are typical for this group: both organelle x and organelle y exhibit either proliferation, hyperplasia, or dystrophy. In each case an increase in the numerical parameters with small organelles (numerical density in particulate organelles, surface density in tubulocisternal organelles) is dominant. Another possibility is that both organelles x and y exhibit either hypoplasia or ageneration or a relative decrease in the numerical parameters of enlarged organelles. Furthermore, hypertrophy or dysplasia, or a relative increase in the volumetric parameter may be present in enlarged organelles x and y. Finally, the pairwise presence of either atrophy or decrease of the volumetric parameter of small organelles may characterize isologous-isometric homology (Fig. 5, Table 1).

(b) Isologous-Diametric Homology Type. In one case organelle x exhibits either proliferation or hyperplasia or dystrophy or a relative increase in the numerical parameter of small organelles, whereas the enlarged organelle y experiences either hypoplasia or ageneration or a relative decrease of the volumetric parameter. A further type may involve hypertrophy or dysplasia or increase of the relative volumetric parameter in organelle x, against atrophy or decrease of the relative volumetric parameter in the enlarged organelle y (Fig. 5, Table 1).

(c) Heterologous-Isometric Homology Type. Here one finds in some cases either proliferation or hyperplasia or dystrophy or relative increase of the numerical parameter in the small organelle x, whereas the enlarged organelle y exhibits either hypertrophy or dysplasia or increase in the volumetric parameter. In

Table 1. Symbolic logic expressions for homology types in quantitative organelle pathology

1. analogous-metrical homology types

AMt = ((((xN& (xZN/xFN)& xVN) & (yP/(yR& –yM)/yY/(yN& –yM&(yZH/yFH)))))/
((xN& (xZN/xFN)& xVN) & ((yE/(yO& yM)/(yN& yM&(yZL/yFL))))/
((xN& (xZN/xFN)& xVN) & (yT/(yR& yM)/yD/(yN& yM& yVH)))/
((xN& (xZN/xFN)& xVN) & (yA/(yO& –yM)/(yN& –yM& yVL)))/

(((xP/(xR&–xM)/xY/(xN&–xM&(xZH/xFH))) & (yN& (yZN/yFN)& yVN))/
(((xE/(xO&xM)/(xN&xM&(xZL/xFL))) & (yN& (yZN/yFN)& yVN))/
((xT/(xR&xM)/xD/(xN&xM&xVH)) & (yN& (yZN/yFN)& yVN))/
((xA/(xO&–xM)/(xN&–xM&xVL)) & (yN& (yZN/yFN)& yVN))))

2. isologous-isometrical homology types

II = (((xP/(xR& –xM)/xY/(xN& –xM&(xZH/xFH))) & (yP/(yR& –yM)/yY/
(yN& –yM&(yZH/yFH)))))/
(((xE/(xO& xM)/(xN& xM&(xZL/xFL))) & (yE/(yO& yM)/(yN& yM&(yZL/yFL))))/
((xT/(xR& xM)/xD/(xN& xM& xVH)) & (yT/(yR& yM)/yD/(yN& yM& yVH)))/
((xA/(xO& –xM)/(xN& –xM& xVL)) & (yA/(yO& –yM)/(yN& –yM& yVL)))/
((xN& (xZN/xFN)& xVN) & (yN& (yZN/yFN)& yVN)))

3. isologous-diametrical homology types

ID = (((xP/(xR& –xM)/xY(xN& –xM&(xZH/xFH))) & (yE/(yO& yM)/(yN& yM&(yZL/yFL))))/
((xE/(xO& xM)/(xN& xM&(xZL/xFL))) & (yP/(yR& –yM)/yY/yN& –yM&(yZH/yFH)))))/
((xT/(xR& xM)/xD/(xN& xM& xVH)) & (yA/(yO& –yM)/(yN& –yM& yVL)))/
((xA/(xO& –xM)/(xN& –xM& xVL)) & (yT/(yR& yM)/yD/(yN& yM& yVH))))

4. heterologous-isometrical homology types

HI = (((xP/(xR& –xM)/xY/(xN& –xM&(xZH/xFH))) & (yT/(yR& yM)/yD/(yN& yM& yVH)))/
((xE/(xO& xM)/(xN& xM&(xZL/xFL))) & (yA/(yO& –yM)/(yN& –yM& yVL)))/
((xT/(xR& xM)/xD/(xN& xM& xVH)) & (yP/(yR& –yM)/yY/(yN& –yM&(yZH/yFH))))/
((xA/(xO& –xM)/(xN& –xM& xVL)) & (yE/(yO& yM)/(yN& yM&(yZL/yFL)))))

5. heterologous-diametrical homology types

HD = (((xP/(xR& –xM)/xY/(xN& –xM&(xZH/xFH))) & (yA/(yO& –yM)/(yN& –yM& yVL)))/
((xE/(xO& xM)/(xN& xM&(xZL/xFL))) & (yT/(yR& yM)/yD/(yN& yM& yVH)))/
((xT/(xR& xM)/xD/(xN& xM& xVH)) & (yE/(yO& yM)/(yN& yM&(yZL/yFL))))/
((xA/(xO& –xM)/(xN& –xM& xVL)) & (yP/(yR& –yM)/yY/(yN& –yM&(yZH/yFH)))))

other cases one finds either hypoplasia or ageneration or relative decrease of the numerical parameter in the enlarged organelle x, whereas the small organelle y exhibits either atrophy or a relative reduction of the volumetric parameter (Fig. 5, Table 1).

(d) Heterologous-Diametric Homology Type. In some cases the small organelle x has either proliferation or hyperplasia or dystrophy or relative increase in the numerical parameter, whereas the small organelle y shows atrophy or decrease in the volumetric parameter. In other cases the enlarged organelle x has either hypertrophy or dysplasia or relative increase of the volumetric parameter, whereas the small organelle y exhibits either hypoplasia or ageneration or reduction of the numerical parameter (Fig. 5, Table 1).

Table 2. Morphometric results: Volumetric, numerical, and surface density of hepatocellular organelles per unit volume cytoplasm. Juvenile control (3-year-old boy); premortem liver biopsy of a 3-year-old boy suffering from glycogenosis type I; postmortem liver biopsy 6 months later

Structural components	Parameter	Symbols in morphometry	Symbols in logic	Control 3 y ♂	Glykogenosis Type I, 3 y ♂		Dimension
					intra vitam	post mortem	
Hepatocytes	Volume	V_{VH}	V	0.85	0.92	0.83	cm^3/cm^3
Nuclei	Volume	V_{VNH}	V	0.050	0.025	0.035	cm^3/cm^3
	Number	N_{VNH}	Z	240	160	150	$10^6 \times cm^{-3}$
Rough endopl. reticulum	Volume	V_{VRER}/V_{VC}	V	0.029	0.017	0.019	cm^3/cm^3
	Surface	S_{VRER}/V_{VC}	F	2.020	0.58	0.53	m^2/cm^3
Smooth endopl. reticulum	Volume	V_{VSER}/V_{VC}	V	0.11	0.03	0.02	cm^3/cm^3
	Surface	S_{VSER}/V_{VC}	F	7.62	0.75	0.44	m^2/cm^3
Mitochondria	Volume	V_{VM}/V_{VC}	V	0.11	0.10	0.12	cm^3/cm^3
	Number	N_{VM}/V_{VC}	Z	385	89	115	$10^9 \times cm^{-3}$
Mitochondrial cristae	Surface	S_{VMC}/V_{VC}	F	1.74	2.05	1.73	m^2/cm^3
Peroxisomes	Volume	V_{VP}/V_{VC}	V	0.006	0.004	0.004	cm^3/cm^3
	Number	N_{VP}/V_{VC}	Z	103	32	42	$10^9 \times cm^{-3}$

(e) Analogous-Metric Homology Type. In these cases either organelle x or organelle y, but not both, show changes of their morphometric parameters, whereas the other organelle shows no significant changes (Fig. 5, Table 1).

2. *Sample Problem: Glycogenosis Type I*

Quantitative organelle pathology applied to the premortem liver biopsy of the three-year-old boy shows a substantial enlargement of liver cells with relative decrease in the entire endoplasmic reticulum and peroxisomes. Furthermore, there is mitochondrial enlargement with increase in cristal membranes. Quantitative morphologic diagnoses show concurrence of small and large organelles, and quantitative pathologic diagnoses show concurrence of proliferation, hypertrophy, and the normal state. These homology types are diametric (Table 4a).

In the postmortem biopsy of the same child, the quantitative morphologic diagnoses show a dominance of enlarged organelles, the result of swelling. In the quantitative-pathologic diagnoses, hypoplasia, and disturbance of new formation (=ageneration) are dominant. Here the homology types are isologous or analogous-metric (Table 4b).

In the glycogenotic adult, quantitative morphologic diagnoses show a concurrence of enlarged and shrunken organelles in the liver biopsy, as in the premortem biopsy of the child. The quantitative pathologic diagnoses show almost exclusively hypoplasia, and the homology types are isometric (Table 4c).

In the hepatocellular adenoma of this woman, a similar picture emerges: the organelles are predominantly small and their quantitative pathologic diagnoses are recognizable as hypoplasia and disturbances of neogenesis. These

Table 3. Morphometric results: Volumetric, numerical, and surface density of hepatocellular organelles per unit volume cytoplasm. Adult control, 25-year-old healthy volunteers (data from Rohr et al. 1976). Liver biopsy from a 22-year-old woman suffering from glycogenosis type I, and biopsy of a hepatocellular adenoma in the same patient

Structural components	Parameter	Symbols in morphometry	Symbols in logic	Controls 25 y	Glycogenosis Type I, 22 y ♀		Dimension
					liver	tumor	
Hepatocytes	Volume	V_{VH}	V	0.79	0.80	0.81	cm^3/cm^3
Nuclei	Volume	V_{VNH}	V	0.056	0.036	0.030	cm^3/cm^3
	Number	N_{VNH}	Z	102	120	165	$10^6 \times cm^{-3}$
Rough endopl. reticulum	Volume	V_{VRER}/V_{VC}	V	0.130	0.026	0.025	cm^3/cm^3
	Surface	S_{VRER}/V_{VC}	F	1.22	0.072	0.873	m^2/cm^3
Smooth endopl. reticulum	Volume	V_{VSER}/V_{VC}	V	0.077	0.033	0.015	cm^3/cm^3
	Surface	S_{VSER}/V_{VC}	F	3.03	0.91	0.38	m^2/cm^3
Mitochondria	Volume	V_{VM}/V_{VC}	V	0.19	0.14	0.08	cm^3/cm^3
	Number	N_{VM}/V_{VC}	Z	230	134	99	$10^9 \times cm^3$
Mitochondrial cristae	Surface	S_{VMC}/V_{VC}	F	4.05	1.78	1.25	m^2/cm^3
Peroxisomes	Volume	V_{VP}/V_{VC}	V	0.013	0.004	0.004	cm^3/cm^3
	Number	N_{VP}/V_{VC}	Z	100	67	47	$10^9 \times cm^{-3}$

Table 4. Mnemonic abbreviations for morphometric data. Morphologic and pathologic diagnoses in terms of quantitative organelle pathology; homology types for the ergastoplasmic-mitochondrial-peroxisomal system. N^* = numerical parameter: corresponding to numerical density in particulate organelles and to surface density in tubulocisternal organelles. V^* = volumetric parameter corresponding to volume density. Q^* = quotient, V^*/N^*, corresponding to volume density. Q^* = quotient, V^*/N^*, corresponding to mean organelle size in particulate organelles and to mean cisternal width in tubulocisternal organelles. $\sim$ = unchanged morphometric values; $\uparrow$ = significantly increased morphometric values; $\downarrow$ = significantly decreased morphometric values

a) Example: premortem liver biopsy of the 3-year-old boy suffering from glycogenosis type I

		Morphometry			Morphology	Pathology	Homology types			
		N^*	V^*	Q^*			M-R	M-P	C-R	C-P
Nucleus	N	$\downarrow$	$\downarrow$	$\downarrow$	S	N				
Hepatocyte	H	$\downarrow$	$\uparrow$	$\uparrow$	G	D				
Rough endopl. reticulum	R	$\downarrow$	$\downarrow$	$\uparrow$	M	N	HD		ID	
Smooth endopl. Reticulum	S	$\downarrow$	$\downarrow$	$\uparrow$	M	N	HD		ID	
Mitochondria	M	$\downarrow$	$\sim$	$\uparrow$	M	T	HD		ID	
Mitochondrial cristae	C	$\uparrow$		$\downarrow$	S	P		HD		ID
Peroxisomes	P	$\downarrow$	$\downarrow$	$\uparrow$	M	N		HD		ID

b) Example: postmortem liver biopsy of the same 3-year-old boy, 6 months later

		Morphometry			Morphology	Pathology	Homology Types			
		N^*	V^*	Q^*			M-R	M-P	C-R	C-P
Nucleus	N	↓	↓	↑	M	N				
Hepatocyte	h	↓	~	↑	M	E				
Rough endopl. reticulum	R	↓	↓	↑	M	O	II		II	
Smooth endopl. reticulum	S	↓	↓	↑	M	O				
Mitochondria	M	↓	~	↑	M	E		HI		II
Mitochondrial cristiae	C	~		~	U	U				
Peroxisomes	P	↓	↓	~	E	O				

c) Example: liver biopsy of a 22-year-old woman suffering from glycogenosis type I

		Morphometry			Morphology	Pathology	Homology types			
		N^*	V^*	Q^*			M-R	M-P	C-R	C-P
Nucleus	N	↑	↓	↓	C	Y				
Hepatocyte	H	↑	~	↓	S	P				
Rough endopl. reticulum	R	↓	↓	↑	M	O	II		II	
Smooth endopl. reticulum	S	↓	↓	↑	M	O				
Mitochondria	M	↓	↓	↑	M	O		HI		HI
Mitochondrial cristae	C	↓		↑	M	O				
Peroxisomes	P	↓	↓	↓	S	O				

d) Example: biopsy of the hepatocellular adenoma in the 22-year-old woman suffering from glycogenosis type I

		Morphometry			Morphology	Pathology	Homology types			
		N^*	V^*	Q^*			M-R	M-P	C-R	C-P
Nucleus	N	↑	↓	↓	C	Y				
Hepatocyte	H	↑	~	↓	S	P				
Rough endopl. reticulum	R	↓	↓	↓	S	O	II		HI	
Smooth endopl. reticulum	S	↓	↓	↑	M	O				
Mitochondria	M	↓	↓	~	U	O		II		HI
Mitochondrial cristae	C	↓		↑	M	O				
Peroxisomes	P	↓	↓	↓	S	O				

e) Example: comparison between juvenile and adult glycogenosis type I

		Morphometry			Morpho-logy	Patho-logy	Homology types			
		N^*	V^*	Q^*			M-R	M-P	C-R	C-P
Nucleus	N	↓	↑	↑	G	D				
Hepatocyte	H	↓	↓	~	U	N				
Rough endopl. reticulum	R	↓	↑	↑	G	D				
Smooth endopl. reticulum	S	↑	~	↓	S	A	HI		II	
Mitochondria	M	↑	↑	~	U	N				
Mitochondrial cristae	C	↓		↑	G	D		HD		ID
Peroxisomes	P	↑	~	↓	S	A				

homology types exhibit isometric changes (Table 4d). The comparison between juvenile and adult glycogenosis shows a dominance of heterologous and/or diametrical homology types (Table 4e).

Discussion

Quantitative morphologic changes proceed within the cell as stereotyped, repetitive patterns. Thus volume and number of cell nuclei exhibit a particular, non-random relationship to volume and number of individual cell organelles. In this manner, within a single cell, the volume and number of organelle x are proportional to the volume and number of organelle y. This is the morphometric basis for the fact that certain enzymes in individual cellular compartments are present in constant proportions (Pette et al. 1962). If one further considers that the mitochondria may be a site of cellular control of drug biotransformations in the endoplasmic reticulum (Cinti and Schenkman 1972), one might suggest that individual cellular compartments, recognizable morphologically as cellular organelles, may be adapted as a whole to the separate functional demands of a cell by way of a common regulatory mechanism.

The physical appearance of such a regulatory mechanism has been demonstrated by Schole's group (Schole et al. 1978). In the center there are radical electrons of the flavoenzymes in the regions of the organelle membranes (mitochondria, ergastoplasm, nucleus) on one side and the SH-glutathione system on the other side. The radical electrons from energy metabolism inhibit the SH-enzymes of synthetic metabolism by oxidizing SH-glutathione, which in turn can activate the SH-enzymes of synthetic metabolism. Eventually, NADH-dependent reductase can again reduce oxidized SH-glutathione (Schole et al. 1978). This type of biochemical regulatory mechanism explains how the cell regulates quantitative changes of the oxidative compartment (=mitochondria, peroxisomes) on the basis of the current status of the synthetically active com-

partment (=RER, nucleus). It also explains why cell organelles respond to lethal and sublethal cellular injury in the form of monotonous reaction patterns (cf. Trump and Arstila 1975; Riede et al. 1980a, b).

What Mechanisms Are Available to a Cell for Structural Reorganization of Its Cytoarchitecture?

a) Neogenesis of organelles with increase in number (Kolb-Bachofen and Vogell 1975; Legg and Wood 1969)

b) Growth of individual organelles with increase in volume (Rohr et al. 1971; Hoppeler et al. 1973).

c) Blockage in organelle neogenesis with decrease in number (Herbener 1976).

d) Growth arrest of individual organelles with normal turnover and decrease in volume (Riede et al. 1971).

The morphologic relationships implied by these mechanisms may be expressed quantitatively and logically in terms of homologies:

Analogous-Metric Homologies are typical of the early or late phase of cellular injury, when cellular damage has first become noticeable in cellular organelle x but is not yet apparent in organelle y (cf. Riede et al. 1980a).

Isologous-Isometric Homologies express a similar type and form of organelle change. In these cases one finds either increased organelle neogenesis or increased organelle degradation or organelle swelling in both organelle x and organelle y. These homology types are found in the resistance phase or at the beginning of the exhaustion phase of cellular injury (Riede et al. 1980a, b).

Isologous-Diametric Homologies. These are often found in the late phase of cellular damage, as an expression of "vita reducta" ("reduced life") (cf. Riede et al. 1980a). Here we find neogenesis of organelle x concurrent with blockade of new formation of organelle y, or swelling of organelle x concurrent with degradation of organelle y. In these cases the cell cannot withstand any further loading.

Heterologous-Isometric Homologies. In these cases one finds either neogenesis in organelle x accompanied by swelling in organelle y, or blockade of new-formation in organelle x accompanied by degradation in organelle y. This homology type is the expression of defective adaptation (cf. Wilson and Leduc 1963) in the resistance phase of cellular injury.

Heterologous-Diametric Homologies. These are often typical of extreme adaptation mechanisms, and are the expression of a "vita minima" ("minimum life") (cf. Riede et al. 1980a). The cell's "point of no return" is at hand (Trump and Arstila 1975). In this homology type there is either increased neogenesis in organelle x with a corresponding blockade in organelle y or swelling in organelle x with degradation in organelle y.

These comprise all the existing homology types which appear in pairwise fashion in quantitative organelle pathology. They may also be carried over into pathologic anatomy, and represent models for corresponding homology concepts which are essential for diagnostic and/or prognostic determination of cellular damage.

What is the Significance of These Homology Types for Pathology?

The answer to this question is given by morphometric studies of patients with glycogenosis type I (glucose-6-phosphatase deficiency) (Spycher and Gitzelmann 1971; Riede et al. 1980c). In the glycogenotic child, the premortem biopsy clearly shows that the diametric homology types dominate in the ergastoplasmic-mitochondrial-peroxismal system, whereas the postmortem biopsy shows only isologous and analogous homologies. This demonstrates that the point of no return has passed in terms of cellular injury, so that the compensatory adaptive mechanisms have been lost (Table 3, Table 4a, b).

In the 22-year-old female patient, glycogenosis type I has taken a different course than in the child (for otherwise the patient would have died earlier) (Spycher and Gitzelmann 1971). The organelles of the ergastoplasmic-mitochondrial-peroxisomal system all exhibit isometric homologies. This indicates compensatory adaptative mechanisms in the liver cells. The same is true for the hepatocellular adenoma in this patient system (Table 3, Table 4, c, d), since both the normal hepatocytes as well as the adenoma cells in this patient showed biochemically both an absolute absence of glucose-6-phosphatase as well as massive glycogen storage.

We are extremely grateful to Prof. Dr. R. Gitzelmann and Doz. Dr. M. Spycher for providing the biopsy material.

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Accepted July 31, 1980