PONTIFICIA UNIVERSITAS GREGORIANA
FACULTAS PHILOSOPHIAE

PHENOTYPE-GENOTYPE DICHOTOMY

An Essay in Theoretical Biology

Auctore

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Dissertatio ad Doctoratum
in Facultate Philosophiae
Pontificiae Universitatis Gregorianae

ROMA 1975

Vidimus et approbamus ad normam Statutorum Universitatis

Romae, ex Pontificia Universitate Gregoriana

die 21 mensis iunii anni 1975

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IMPRIMI POTEST

Romae, die 24 septembris 1975

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Con approvazione del Vicariato di Roma in data 30 settembre 1975

TYPIS PONTIFICIAE UNIVERSITATIS GREGORIANAE — ROMAE

Acknowledgments

The general conceptual texture of this essay is determined by many factors. First of all I am greatly indebted to my professors and colleagues from the Department of Human Physiology, School of Medicine, Warsaw, who initiated me into the intricacies of the methodology of biological research, and to the professors of the Jesuit Philosophical Faculty in Cracow who introduced me to Aristotelian epistemology and ontology.

I wish to express my deepest gratitude to the director of this doctoral thesis, Fr. Jerzy Szaszkiewicz, S.J., of the Gregorian University, Rome, who patiently read one draft after another and provided me with invaluable criticism and guidance. He is responsible for whatever coherence and lucidity there may be in this essay.

During the first stage of this work when I had to collect and select the necessary empirical material, my research was made much easier because of some rather special privileges and facilities I enjoyed at the British Museum's (Natural History) General Library where Mr. W. Halliday was most obliging. At the Institute of Genetics of the University of Rome Prof. Dr. Giuseppe Montalenti kindly agreed to grant me similar privileges, and the librarian, Mr. Mario Vartolo, offered me all the assistance needed.

All the more complicated drawings were done by my Mother from the sources indicated.

The final text of the essay was read by Prof. Dr. Vittorio Marcozzi, S.J., Prof. Dr. Angelo Serra, S.J., and Dr. Giovanni Blandino, S;J. I treasure their critical remarks, although unfortunately I was not able to use all of them while preparing this text for printing.

I have to express my special thanks to my friends Alfred Buttigieg, S.J., and Benjamin Sargent, S.J., for most fruitful discussions of the subject. Ben has also spontaneously carried out the laborious work of making proofs of the whole text.

Sister Mary Agnes Ryan, Mr. Speer Ogle, Mr. Henry McConnachie and Mrs. Harriet Rosenberg have rendered a great service by amending my private English into a closer approximation of common English usage. Harriet Rosenberg has also cheerfully and patiently typed the whole text from my hieroglyphic manuscript.

The publication of this essay would not be possible without the generous subsidy from the Augustinus Bea Stiftung, Munich, to which I am truly grateful.

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CHAPTER ONE
GENERAL CONSIDERATIONS ON THE OBJECT OF STUDY

1.1 Introductory remarks

During the last decade or so, several voices were raised to encourage a closer philosophical investigation of theories currently accepted in the natural sciences. Feyerabend, for instance, has pointed out how the lack of a due theoretical "opposition" and a monopolistic concentration upon one "orthodox" theory may lead to ignorance of facts which could test it and to a certain negligence or even reluctance in the search for them. A theoretical system is "successful" for no testing criteria were postulated, and facts were removed. "...At this point an 'empirical' theory...becomes almost indistinguishable from a myth" (1963/25-8).

Feyerabend thinks that the first step to overcome the above objectionable state of affairs should consist in the formulation, or the invention of a new metaphysics, because (as he puts it): "elimination of all metaphysics — is liable to turn theories into dogmas" (1963/37)[1]

How does one carry on such an obviously ambitious program? Are philosophers able to help the scientists in this task? As Bunge rightly states:

> "Philosophers, with the sole lancet of logic, are not equipped to deal with facts and should not try to compete with scientists" (1963/6).

At the same time, though, he complains about the "growing gap between humanistic and the scientific cultures" in a context which puts philosophers on the humanistic side of this gap. Vandel is even more decisive in his wording:

> "On doit regretter que la plupart des philosophes formés aux disciplines purement 'littéraires' remplisse bien mal leurs fonctions. Ignorant ou méprisant 1'énorme apport engendre par la recherche scientifique et le renouvellement profond qui en decoule ils demeurent en dehors de la pensée et de la vie de notre temps." (1965/377)

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[1] See also the ironic and possibly a bit exaggerated remark of Chargaff's: "The fashion of our times favours dogmas. Since a dogma is something that everybody is expected to accept, this has led to the incredible monotony of our journals. - Most of these papers are very competent; they use the same techniques and arrive at the same results. This is then called the confirmation of a scientific fact. Every few years the techniques change; and then everybody will use the new techniques and confirm a new set of facts. This is called the progress of science." (1965/19). Superficially this caricature is quite unjust. But, in reality, the investigational techniques determine to a great extent the way we can look upon life phenomena, and the precision and repetitivity of the results obtained in this way is not always proportionate to their relevance in solving fundamental problems of life. See also Needham's scheme of "limiting factors" which determine the scientific investigation in natural sciences (1959/231) and Hughes 1959/139.

The crucial problem raised by the above statements may be reduced to one question: is biology in need of any help from the "professional" philosopher? The history of the natural sciences does not provide us with a univocal answer. We know, for instance, that some fundamentally erroneous ideas, such as the theory of preformation, or more recently, the biocolloidal theory[2], were formed or invented by empiricists. They have now been discarded as completely unacceptable, not because of a philosophical criticism, but because the progress of empirical knowledge has made them ridiculous. In both cases a false theory had survived for a considerable period of time, that is, at least two or even more generations of biologists. These errors pervaded several decades of scientific investigation and were continuously promulgated by indisputably respectable textbooks[3]. Would they have been discredited earlier if a due philosophical analysis had been applied at the right time? (See Needham 1959/238).

Another problem should be raised here, namely, the problem of the real nature of the "biological way of thought." In spite of their stubborn denials, one might suspect that the biologists, in their way of thinking, are not so radically different from philosophers. Sommerhoff distinguishes three groups of contemporary biologists:

> "the first and largest group is of those who — explain life away. The second group descends to the vague language of philosophical speculations...The third group...comprises those who are vaguely aware of the bankruptcy of both the above schools of thought, yet do not know how to break away, and in consequence fight shy of the general problem of life altogether..." (1950/3).

Sommerhoff's first and second group of biologists is quite obviously philosophically minded, and it might well be that the third one *is* even more aware of the philosophical problems than the first two. Anyway, the awareness

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[2] In the chapter entitled: "The Dark Age of Biocolloidology," Florkin (1972/ 279-283) writes: "...it is surprising to realize that the concept of biocolloidology based mainly on studies of degraded or impure preparations (and formulated by Graham in 1861 - PL) remained accepted in certain circles until, well into the forties..."

[3] Both above-mentioned erroneous theories have had a decisive role in shaping both the progress of biological sciences and more generally upon philosophical attitudes towards the problem of-life. Preformation theory explaining away epigenetic phenomena has helped to eliminate the Aristotelian concept of living being, while the biocolloidal theory has contributed in a decisive manner to the speculations upon the possible origin of life and upon the role of random, chance events in processes of life.

of the general metaphysical and/or epistemological problems raised by the alternative interpretations of biological reality is certainly not confined or limited to a small group of professional philosophers. It is rather obvious that the majority of biologists are in fact working upon two levels of thought, observational, that is, purely empirical, on one hand, and the speculative, interpretive and generalizing on the other. If Van der Steen and Jager complain about the "deplorable gap between biology and philosophy" (1972/265) and call for some new forms of philosophical analysis in biology, they simply want to encourage and make more explicit the rather hidden undercurrent of speculations which are present in the mind of biological scientists, but, because of some anti-metaphysical prejudices or misunderstandings are treated as something embarrassing, unfair or illicit.

The main purpose (endeavour, aim) of our study will consist in showing that some philosophical and metaphysical principles are currently used in the domain of apparently empirical biological study such as modern genetics. We will try to show how the principles determine the origin of some genetic postulates, the interpretation of evidence and the selection of alternative speculative solutions.

1.2 The problem of the proper limitation of the object of study

The selection of a right object of study is of greatest importance for the successful execution of our aim. In this respect two main questions have to be answered.

First, being aware of the immense empirical evidence, collected by biological investigation, we have to admit that it would not be possible to make an analysis of the biological speculative "workshop" without limiting our attention to a part of this evidence. But how do we select this evidence without eliminating more general, "philosophical" issues which are of crucial importance for our study?

Secondly, we have to take into account that contemporary biology constitutes a sort of a "whole" so that the direct evidence collected in one field of biological study is interpreted in the light of data provided by other fields. Would it be possible to isolate a limited area of biological study and to investigate it separately from the rest? Of course, a biologist does it quite often, and he *has* to proceed in this way. But a philosopher should be aware in some way of all the problems raised by a concrete object of study. How do we overcome this apparently unsurmountable difficulty?

The first question concerns the limitation of empirical evidence.[4] The second question is the limitation of the theoretical framework operating in biology.

We will solve the first question by limiting ourselves to an analysis of empirical evidence concerning "basic," "fundamental" biological phenomena, which are essentially identical both in unicellular and in multi-cellular organisms. We will not enter into discussion of such complex phenomena as, for example, neural or hormonal control systems which are observable in a restricted group of organisms and are dependent upon more basic ones, those of intracellular metabolism, cellular division, differentiation. . .and so on. Regarding the second question, i.e., the theoretical aspect of our problem, we will limit our analysis to the theory of genetics and the phenomena of ontogenesis, leaving aside all the phylogenetic speculations and the related empirical evidence.

To begin with, we will discuss in some detail the reasons which justify such a limitation of the object of our study.

1.3 Restriction of empirical evidence

During the '50s and "60s, considerable progress was made in making explicit the speculative background of biological research.[5] Two tendencies may be recognized in the vast material which was written and published on this subject.

One is the ambitious effort to include the whole range of phenomena presently observed in the enormous variety of living beings and the problems raised by them. Many authors attempt to solve by a more or less simple principle the phenomena ranging from the reproduction of viruses up to the phenomena

[4] Pattee (in: Lang 1969/14) admitting that "the significant facts of life are ...more numerous than the facts of inanimate matter" writes: "...physicists still hope that they can understand the nature of life without having to learn all the facts." The same hope underlies our own study. But we will attempt to discover a reasonable foundation of this hope.

[5] The bibliography of essays on philosophical problems of biology was compiled up to 1967 by Robert (1968). Some important, positions, however, are missing there. We might quote, for example, Sellars (1922), Mainx (1955), Lingerer (1941, 1966) Gerard (1958) or Pringle (1963). Since 1967 a number of publications on this problem have seen light. We should quote such greater works or compilations of articles as Waddington (1968, 1969, 1970, 1972), Koestler and Smythies (1969), Blandino (1969), Rensch (1968), Pantin (1968), Simon (1971), Black (1972), Ruse (1973), O'Neil (1969), Miller (1973).

of human behaviour[6]. This approach scans to have at least one serious disadvantage. In the case of specialized organs as, for instance, the central nervous system, any serious approach has to keep in mind the interdependence between the different levels of its structure, the developmental processes and the functional dynamics. This implies the awareness of specific biochemical evidence, such as specific cytological evidence, specific anatomical and physiological evidence and finally behavioural evidence, too. This evidence includes not only "natural" events but pathological and laboratory artifacts as well. Even this is still only fragmentary.

The evidence concerning the simplest forms of life, although also fragmentary, presents a far more limited sphere of facts. On the other hand, there is no convincing reason why the process of philosophical investigation should necessarily include all the levels of life. The life of blue-green algae, for instance, is not dependent upon the nature of human behaviour. On the other hand, some biological or biochemical processes observed in human cells are not discernible (in their form and dynamics) from the processes observed in blue-green algae. (See Green § Goldberger 1967/383-399). So it seems that we may legitimately exploit the biological evidence collected during the observation of all existent forms of life, without including in our discussions and interpretations these facts which distinguish the higher forms of life from tie lower ones. In our study we will deliberately refrain from trying to produce an all-embracing concept of life phenomena. We belive that this approach, although limited, may still be treated as a truly philosophical reflection on the nature of life.

1.4 Restriction of theoretical conceptual framework

Since the theory of evolution has become the basic point of reference for biological study and interpretation of its results, every analytical study of life phenomena tends to start from a discussion of the evolutionary

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[6] Caws (1964), for example, believes that such concepts as "feed-back," "trial and error" concept and random interactions of material entities might constitute the basic set of problem-solving ideas. Thorn (1968) puts forward an explanatory model based upon a mixture of relatively simple geometrical forms and a rather mysterious dynamism which apparently is neither biochemical (or more generally physical in the current sense of the word) nor biological (physiological, developmental) for it was obviously thought out in order to explain them or to replace them. Black (1972) considers the idea of information as crucial to the understanding of biological, pathological and psychological phenomena. Many authors make recourse to the idea of "organization"or "control system" (see, for example, Reiner (1968). But, as we will see later on, it is extremely difficult to judge which of these and other similar concepts are really explanatory ones and which are nothing more than redescriptive ones.

conceptual framework, of its empirical origins, its conceptual developments and their applications[7].

"...Abiology that forgets species, natural selection, interaction of populations, is a sterile biology..." (Goddard 1958/148). This, or analogous opinions, are widely accepted among biologists and philosophers of biological sciences. Both static[8] and dynamic[9] features of organisms should, according to this opinion, be explained or even analyzed in the context of mechanisms of natural selection and, more generally, within the conceptual framework of evolutionary ideas[10]. As Mayr stated: "There is hardly any structure or function in an organism that can be fully understood unless it is studied against this historical background" (1968/43). Biology is thus considered as an essentially historical science. But although this contention is certainly true, its validity is rather restricted. The "full" understanding may mean the "ultimate" understanding, and of course in this sense chemistry and physics are historical sciences too, for we could legitimately ask how and why the presently existing atoms or molecules have appeared in our universe. But there is no valid methodological principle which would forbid us to analyze the presently existing organisms without the reference to their "historical" origin. "The real problem of causality, in so far as the 20th century still admits the concept of causality, is related to the materials with which genetics deals,...Genetic concepts...were not in their origins influenced by concepts of evolution except in the remotest sense...Mendel was not concerned with phylogeny, nor even with embryos" (Oppenheimer 1969/215). It seems that Beckner is quite right when he writes: "phylogenetic explanation must employ a general theory of heredity," stating in this way the epistemol-ogical primacy of genetical studies over the evolutionary ones (1959/101; see also Woodger 1967/393-5, 402; Needham 1959/239-40).

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[7] Waley explicitly states that for instance "the biochemist is profoundly (sometimes unconsciously) affected by the unifying concepts and guiding principles of biology, such as evolution and natural selection, the wholeness and purposive-ness of organisms or the.stability of internal environment...(1969/139).

[8] See, e.g., Kantor (1962/218): "We know, for instance, that the size and structure of the isolated bone is a function, in a mathematical sense, of a large number of factors which have operated in its evolution."

[9] Cfr., e.g., Caspari (1964/143): "Function must be understood as a consequence of natural selection. The question for the function turns out to be basically an historical one —"

[10] See, e.g., J.T. Bonner (1963/147); Caws (1965/313); Smart (1968/102); Bonner (1971/xix); Ayala (1970/1-15); Cowden (1972/!Ś3-109).

Another reason might be mentioned here in favor of eliminating the evolutionary concepts at this preliminary stage of philosophical analysis. In a sense it was already traced in Beckner's above-mentioned argumentation, but we will try to make it more explicit. The concept of evolution presupposes the following investigational steps:

10. Some "dead" mineral or organic objects must be recognized as the parts or remains of the once-living form[11].
11. The structural, functional and developmental reconstruction of that form has to be done.
12.The existence of the "evolutionary" trend has to be discovered on the basis of the reconstructions accomplished on the previous step.
13.Contemporary, directly observed adaptive non-evolutionary mech anisms must be rejected as a possible explanation of the-observed regularities, or trends.
14. A postulatory mechanism of an evolutionary theory must be pro posed, and it should be adequate to the reconstructed phenomenology of the ev olutionary trend.
15. The problem of the verification of those postulatory mechanisms should be properly solved.

In other words, evolutionary reconstructions and interpretations presuppose an adequate concept of the contemporary living forms. But strikingly enough, almost every essential and fundamental problem of anatomical, physiological or biochemical phenomena is dismissed too often by the statement: "they should have evolved in such a way." A kind of vicious circle has been created in which a rather dogmatic belief in the all-explaining power of some speculative and abstract ideas and extrapolations prevents any deeper analysis of the real questions of life[12].

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[11] "...it is undeniable that as far as the fact and course of evolution is concerned, the fossil record is irreplaceable evidence..." Ruse(1973/118).

[12] For example, Smart (1968) in the chapter entitled "Explanation in biological sciences" confines himself to the discussion of taxonomy, theory of evolution and cosmic biology. This sort of theoretical approach may provoke a completely false idea about the main source of empirical evidence upon which a valid explanation of life phenomena should be based.

Even taking for granted the validity of the subtle mutual relationships between population genetics, morphology, embryology classification and paleontology, as discussed by Ruse (1973/48-52), the epistemolo-gical priority of genetics over the evolutionary concepts, stressed by Beckner and Oppenheimer, seems to be certain enough to justify our decision to limit ourselves to the contemporary (non-evolutionary) dimension of the phenomena of life[13].

The conclusions we may reach at the end of our analyses will thus be limited to the contemporarily observable phenomena, and to the lowest level of the life processes.

The above limitations are a sort of inevitable compromise conditioned by an enormous amount of data on the one hand, and, on the other, the desire to ground our philosophical analysis upon empirical evidence.

1.5The distinction between "question-raising" and "question-solving" evidence

Two categories of "basic" concepts should be distinguished at the beginning of philosophical analysis. One category will serve to state in a concise, abstract way the main elements of the "question-raising" descriptive evidence. The second one helps to state the main elements of the "question-solving" evidence (explanatory postulates). The same term, e.g., the concept of "feed-back" may be used in both senses. A structure may be described in terms of a "feed-back" system, and so be treated *as* a "question-raising" descriptive evidence which postulates a further search for the right explanation of its origins. The same term, the same concept may also be used as a "question-solving" concept, i.e., in such a context in which the stability of a system is confronted with its unstable environment.

In other words, one set of "basic" concepts (and terms) refers to the sphere of empirical premises, while the other refers to the sphere of the conclusions discovered, or produced by the process of interpretation and elaboration of primary, empirical evidence.

In the light of the preceding considerations, the object of our study might best be formulated as follows:

a) To make explicit some epistemological and possibly ontological axioms which operate within the sphere of the speculative "workshop" of bio-

[13] See Oppenheimer (66/47-49) . She analyzes the "Biological Fallacy" which consists in explaining the ontogeny in terms of phylogeny"

logical scientific investigation. This is based, of course, upon an earlier conviction that such axioms are really operating within biological scientific thought.

b) The search for epistemological and ontological axioms will" be done on a selected topic, within a limited sphere of biological investigation. This will enable us to observe how direct empirical evidence is collected, how it is abstracted from the apparently random sphere of the natural world, and which elements, of this evidence constitute a "question-raising" data. This question-raising element provokes and directs to a certain extent the search for further evidence. We will also try to discover what sort of criteria are applied before an evidence is considered as "question-solving." The nature or the conceptual structure of several concrete scientific postulates used in this process will then be analyzed together with the criteria put forward to verify them. Finally, the coherence of the overall conceptual scheme will be critically evaluated.

The topic selected for our study is constituted by a set of two complementary concepts elaborated by modern genetics. This set is usually referred to as "phenotype" and "genotype." In a concise manner we will try to demonstrate the place and the significance of these two concepts within the more general context of biological ideas.

1.6 Phenotype-genotype dichotomy — the formal object of study

> "The world contains, among other things, material bodies whose structure and behavior have earned them the designation of living. For Aristotle the difference between animate and inanimate objects consisted in the possession of psyche, the principle of life. Biology is the science which attempts to define and elucidate that principle and to render intelligible the things that have it." (M.A. Simon, 1971/1).

The principle which makes the difference between the "animate" and "inanimate" object is no longer called psyche. It is now called the genotype. Genetics and molecular biology attempt to investigate and elucidate the nature of this principle. The most essential difference between the Aristotelian psyche and the genotype of geneticists is this. The genotype is believed to be a complex chemical molecule. The Aristotelian psyche has, to the contrary, had some curious, specific properties which cannot be reasonably attributed to any observable, spatial beings. We will not enter into the discussion of the reasons which led Aristotle to postulate the existence of such a strange entity, nor will we analyze the properties of his psyche. We will concentrate instead on

the reasons which led to the postulate of the genotype's agency. We will investigate the empirical evidence which not only started the whole idea of the genotype but also verified it.

The concept of the genotype is crucial not only to the proper understanding of the modern definition of the living organism but to the problem of the theory of evolution, too. All the environmental influences affecting an evolving population are divided into those which affect the genotype (the mutations) and those which affect its counterpart, the pheno-type (the natural selection). The concept of the genotype is also fundamental in the theoretical and experimental attempts to re-create life from inorganic matter.It is commonly accepted-that the genotype had to be formed during the earliest phase of the life processes[14].

The centrality of the conceptual framework of the "phenotype-genotype" in modern biology is not the only reason for a philosophical analysis of these concepts. For a philosopher, these concepts are of utmost interest because of some epistemological problems involved in their formation, and because of some important ontological consequences provoked by their irreduci-bility. Their origins and their meaning illustrate the "speculative workshop" of biology, on the one hand, and the specificity of its object of study, on the other. So, in a way, the analysis of the origin and the operational value of the "phenotype-genotype" dichotomy throws light upon the process of reasoning accepted in biological sciences. "This point is important from the epistemological point of view.

The problem of the "genotype-phenotype" dichotomy might suggest, from the ontological point of view, a revival of a certain dualism which was long ago expelled from the biological mentality. The dualism was always considered a philosophically touchy idea, and its consequences were quite clear to Haeckel when he wrote:

> "Where teleological Dualism seeks the arbitrary thoughts of a capricious Creator in the miracles of creation, causal Monism finds in the process of development...the necessary effects of eternal immutable laws of nature."[15]

Unlike the vitalistic "forces" and "agents," the genotype belonged for over a half-century to the basic concept's of biology, although for most of

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[14] Cfr. Haldane (1965), cited by Bernal (1967/150-1) and Herskowitz (1973/575-6); cfr. also Pattee (1965/365).

[15] Haeckel, History of Creation, 1868; cited by Hall (1969,11/326).

this time its nature remained no less mysterious than the nature of the former discredited ideas[16]. How the idea of the genotype was finally reduced to the macromolecule of DNA and to what extent this reduction might be. considered as satisfactory will constitute one of the main questions we want to answer in our study.

After this brief introduction into the subject matter of our study we will have to discuss the general background of biological contemporary methodology. We will also have to analyze and define some basic, elementary descriptive categories commonly used in this field in order to reduce the danger of an elementary terminological misunderstanding.

1.7Some general considerations on the methodological background of modern biological theories

The contemporary biological investigation does not start in a conceptual void. Scientific approach towards phenomena of life is determined today (as it has been before) by an extremely complex and yet fragmentary empirical and speculative knowledge inherited from previous generations of scientists (see Kerkut 1960). It is simply impossible to enumerate all the more or less explicit presuppositions, opinions and pre-scientific beliefs which determine, to a certain degree, the process of scientific discovery in biology, and which (consequently) influence its conclusions and theories. The methodology of the natural sciences is poorly understood for two main reasons. First of all, the theories of scientific methodology are critically discussed by people who seldom tested their conclusions in the process of the actual scientific investigation (Vandel 1965). On the other hand

> "...a scientist's account of his own intellectual procedures is often untrustworthy. 'If you want to find out anything from the theoretical physicists about the methods they use,' said Albert Einstein, 'I advise you to stick closely to one principle: don't listen to their words, fix your attention on their deeds.'" (Medawar 1969/10).

The consequences of this fact are further amplified by several onto-logical and epistemological premises which might influence the contemporary way of thinking. We have already mentioned the monistic principle[17]. We might also

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[16] J.H. Muller in his lecture on "the Gene" states: 'TTie gene has sometimes been described as a purely idealistic concept, divorced'from real things, and again it has been denounced as wishful thinking on the part of those too mechanically minded. And some critics go so far as to assert that there is not even such a thing as genetic material at all, as distinct from other constituents of living matter" (Proc. Roy. Soc., B 134 (1947), p. 1).

[17] The monistic doctrine, although quite successful upon the level of "vegetative" life phenomena is more restricted in the case o'f psychic phenomena (cfr. Rensch (1971/29-34); Wocdger (1967/204-7); Ungerer (1972/312).

add the widespread belief in the explanatory supereminence of quantitative over qualitative descriptions[18]. There is a conviction that the phenomena observed upon the lower observational scale (microscopic, biochemical ones) are, in a way,more "real," valid or fundamental than the phenomena observed upon the higher scale[19]. There is also the opinion about the unity of the so-called "Universe,"[20] and finally the persuasion that there is a "hidden order" somewhere at the "bottom" of reality.[21]

These ideas constitute the complicated essence of the controversy concerning the "reductionistic" approach towards the phenomena of life. They cause constant polemics between biologists themselves. The solution of these controversies does not seem to be close- at hand.[22]

The nature and origin of all this speculative, theoretical background is too complex to be analyzed here. We would never start our analysis of the genotype-phenotype conceptual framework if the solution of any single one of the above problems had been considered as a preliminary condition to our study.

The only thing we can do is to reflect upon the meaning of terms

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[18] This belief is based first, upon the assumption that physics is the "primary" science, and, secondly, that the "standard of our knowledge/primary[3] basic=physical - PL/ is found in its approximation to the nudae "quantitates" (Weyl 1949/139; cfr. also Taton 1972/172).

[19] Cfr., e.g., Schaffner (1967); Stent (1968); Dobzhansky (1969/171-2); J.T. Bonner (1971/xvii).

[20] Cfr. Sellars (1922/176-191); Pantin (1968/102); Bohm 1969/29); cfr. also the remark of C.D. Broad cited by Woodger (1967/395): "it is much more disastrous to slur over differences which are really irreducible than to recognize differences and wrongly think them to be irreducible. If we make the latter error we still have in hand all the data for the solution of our problem, and we or others will solve it when we have pushed our analysis a little further. But, if we make the former mistake, our data are incomplete and the problem cannot possibly be solved until we have recognized this fact." Cfr. also Bunge (1963/9) who writes: "a handful of pseudoproblems may be less dangerous than the killing of a single genuine problem."

[21] Cfr. Kantor (1962/213); Toulmin (1967/126 ff.); Bunge (1963).

[22] From the historical point of view, it is extremely interesting how persistent are the main elements of the controversy. Cfr., e.g., Schaffner (1969/ 325-48); Florkin (1972/177); Sommerhoff (1950/3); Commoner (1961); Polanyi (1968); Weiss (1972/40 ff.); Caws (1965/308) confesses that the failure of the realization of the reductionistic program "might be simply a function of the complexity of the task, or it might on the other hand indicate an obstacle in principle."

frequently used in the bio-theoretical speculations such as: homogeneity, heterogeneity, randomness, randomization, order, movement, change, influence, whole, part, organization, control and the like. Even the notion, of "environment" has to be analyzed in order to avoid, or rather diminish, the ambiguity and misunderstanding. Some elementary terminological clarifications will be made in the latter section of this introductory chapter. The other concepts will be analyzed in the main part of our essay.

1.8Sources of information about the empirical evidence

There is another methodol9gical problem we have to discuss at the very beginning of our study. It is the problem of sources of information about the empirical evidence upon which our study will rely.

We will be concentrating our attention upon the biological phenomena which were considered as "question-raising" or "question-solving" in the context of the genotype-phenotype dichotomy. In other words, we will search for the evidence which caused the formulation of our concepts and which was brought in to test their validity.

At this point a question may arise whether a philosopher might rely upon "second-hand" information reported in a textbook, or should he rather go back to the original report of the scientist who actually observed a given phenomenon or proposed a new interpretation or theory. It seems that the answer to this question is complicated by some facts and regularities which we will now discuss in some detail. From one point of view, a textbook or monograph is more reliable than a single experimental or observational report. A textbook or a monograph, having been written by a specialist in a given field, constitutes in a way a sort of "sieve" in which only the evidence which was repeatedly tested remains as the material for further progress and study. Let us illustrate this situation with two examples. When the DNA molecule was identified with the genotype, the postulate of its stability reflected upon the opinion about the DNA's ijnmunity from any external influence (with the sole exception of random mutations). In this theoretical context, a single report suggesting that the DNA molecule undergoes repair would not be persuasive enough. Some more or less complicated interpretations of the empirical evidence would be preferred to a simple acceptance of the fact. If, on the other hand, the idea of the DNA repair finds its way into textbooks or monographs, the rank of this observational datum is higher. Any theoretical interpretation based upon a fact found in such a source is more reliable than otherwise. The

similar situation, mutatis mutandis, might be illustrated by the case of reverse transcriptase discovery.[23]

It would be wrong, however, to think that textbook information is the only empirical report upon which a philosopher might analyze the nature of scientific observational procedure or scientific reasoning. Often the "first-hand" report is needed to evaluate the meaning of an unqualified generalization stated in a textbook. In order to avoid the speculative artifacts, a critical philosopher will have to analyze the empirical sources in order to get the right idea of the facts. Let us consider the following concrete example. Berill writes: "Highly organized cell components when (artificially, in vitro - PL) depolymerized (disrupted - PL) are capable of re-constitution through self-assembly process" (1971/55). Similarly, in a reference to a concrete case of the 30-S RNA complex particle[24], Mahler and Cordes wrote: "...all the requisite information for the assembly of this particle is implicit in its components..." (1971/924). But if we consult the first-hand source (see Fahnestock et al. 1973/179-218), we see that (1) the self-assembly"occurs in an environment which parameters (presence of ions, the level of pH, the level of temperature...and so on) have to be controlled in a non-random way; (2) that the speed of the "self-assembly" can hardly be compared with the speed of the same process in vivo, and (3) that the tests of the "functionality" of the re-assembled complex are relatively crude. So it is impossible to evaluate to what extent the *in vitro*

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[23] The so-called Central Dogma of molecular genetics consists in the postulate of the "one-way" transcription of information between desoxyribonucleic acid (DNA) and the messenger ribonucleic acid (mRNA). The transcription from mRNA to DNA was then theoretically excluded. In 1970 Temin and Baltimore discovered that in some tumor viruses the reverse transcription actually does take place. This fact, however, was almost immediately interpreted as an example of sheer pathology, to this extent that the assay for the reverse transcriptase was expected to become a diagnostic tool for cancer. The state of mind among biologists in reference to the Central Dogma and the reverse transcriptase discovery might be illustrated by the following quotation: "Lancet [English medical journal of international renown - PL] in an Editorial (1970) ...ascribe to a noted molecular biologist the remark that he would 'become a theologian[1] if reverse translation were discovered" (Hahn, 1973/9). Since that time a number of undisputable data on the presence of reverse transcription enzymatic mechanisms in normal cells have changed the general ideas about the universal validity of the Central Dogma. The reverse transcription mechanism has now been introduced into the text of modern manuals of genetics. (See "Beyond the Central Dogma," Nature New Biology, 230 (1971) 97-8; Hersko-witz 1973/60, 63).

[24] The 30-S is a complex nucleoprotein particle which forms, together with 50-S particle, the cytoplasmic organelle called ribosome. Ribosomes participate in the complex process of deciphering the information carried by messenger RNA and joining together into a non-random polypeptide sequence the presumably random set of aminoacids carried by their specific tRNAs.

re-assembly process recalls the respective actual series of chemical events in vivo. It is also impossible to be sure at the moment whether in vitro reassembled 30-S RNA unit would be really "usable" in vivo. But even this lack of precision (possibly unavoidable, because of the limited space in a textbook) would not be dangerous if the statement about the re-assembly of macromolecules was not put in close relation to the explanation of the reassembly and the regeneration of the unicellular and multicellular organisms. The latter case presents clear-cut, precise and certain evidence of the re-assembly capacities (see, e.g., Holtfreter 1945, 1947; Akira Wada § Pollak 1969; Gather 1971; Gierer et al. 1972). The former case is still known incompletely and its relation to the analogous processes in vivo is uncertain. If the terminology is the same in both cases, an unavoidable misunderstanding arises.

For this reason some lengthy and detailed analyses of empirical evidence are sometimes necessary in the process of a philosophical analysis of an empirical theory.

2.9 Basic descriptive concepts

The ambiguous terminology creates one of the main obstacles to progress in understanding the problem of life in general and the problem of heredity in particular. The notion of "organization," for example, so widespread in the context of biological explanations and theories, remains today as vague as it was over a hundred years ago .(see Woodger, 1967/288ff.; Fruton, 1972/503). Sommerhoff complains that although many authors consider "organization as a main distinctive trait of living organisms" (as opposed to inorganic matter), still nobody "manages to tell us in precise scientific terms what exactly is meant by 'organization,' and what exact spatio-temporal relationships distinguish a higher form of organization from a lower" (Sommerhoff, 1960/12).

Ten years later Weiss pointed out that the principle of cell activity "suffers not so much from outright neglect as from being frozen into literary symbols (e.g., 'control,' ' organization,' ' information,''coordination,' ' regulation,' etc.), the resolution of which-into objective terms has been bypassed far too long" (1961/2).

Quite recently Bonner wrote: "...the notion of organization. This term has always disturbed me because it covers everything; what does not have organization?" (1971/xvii).

Being aware of the tremendous difficulties hidden behind the whole problem of the structure and dynamics of living things, we will not attempt to discuss the problem of organization directly, but to prepare the ground for a more detailed analysis by defining some of the more elementary terms, such as homogeneity, heterogeneity, randomness, order and the like.

1.10The descriptive notions of order, homogeneity and heterogeneity

The term "order" (in its descriptive sense) belongs to a larger group of apparently related terms such as "regular," "non-random," "symmetric." These are opposed to such terms as "disorder," "irregular," "random," "lacking in symmetry."

Both sets of terms are distinct from the term "homogeneity." Observational homogeneity may signify:

14. An objective "sameness" of parts in an object under observation (objective homogeneity);
15. a subjective (observer's) incapacity to distinguish the differences actually existing among the parts of the object (subjective homo geneity) .

We cannot distinguish between the objective and subjective homogeneity without introducing the concept of the observational scale range. Our sense organs have a limited observational scale range, which can be extended by such observational devices as telescopes or microscopes. As Smith puts it:

> "Each 'level' is what we see at certain resolutions, and corresponds to the matching of only those structural elements that can be resolved without too much detail at a single effect viewing distance. Both the narrow cone of sharp vision and the simplicity of the fact or idea-patterns that we can have in our minds at any one time introduce a basic indeterminacy in our knowledge of the world. Yet we can sequentially apply this attention span to many different things on one scale. We can use the microscope to diminish, or distance to increase the effective scale and to some extent, through a combination of memory and forgetfulness, or a wilful lack of precision, we can relate all these views and find larger patterns" (Smith 1969/80-81; see also Yates et al, 1972/121).

The "scale" of the actual observation is to a certain extent *arbitrarily* selected, and so the set of recognizable details of this arbitrarily selected scale cannot be uncritically accepted as a "natural pattern" nor used

to decide ultimately about our judgment on the essential characteristics of the object.

> "Selection of strata in which a given system is described depends upon the observer, his knowledge and interest in the operation of the system, although for many systems there are some strata which appear as natural or inherent" (Mesarovic § Macko, 1969/32).

An object is thus objectively homogeneous within a given observational scale range if any of the arbitrarily selected parts of it manifest the same observational properties within this scale range.

Objective homogeneity is opposed by objective heterogeneity. Consequently, the idea of heterogeneity implies the intrinsic differences within the observed object. Heterogeneous objects may be "ordered," "non-randomly organized," "regular," "showing intrinsic symmetry," or, to the contrary, they can be "disordered," "randomly organized," "irregular," "lacking in symmetry." Bohm (1969/21) points out that the "constitutive [intrinsic] differences" determine the essence of the order of whatever we are talking about. He distinguishes also the "distinctive differences" which determine how one order can be distinguished from the other.

So it seems that heterogeneity (complexity) of an object is a necessary but not sufficient condition of its intrinsic "order," "regularity," "non-randomness," "symmetry," "disorder," "randomness," "lack of symmetry."

From the point of view of heterogeneity (complexity), an "irregular" object is more complex than a regular one, a non-symmetric more heterogeneous than a symmetric one, an "ordered" or "non-randomly organized" one less complex than a "disordered" or "randomly organized."

The descriptive idea of "order," "regularity," "symmetry"...and so on seems then to imply a certain level of repetitivity of heterogeneous descriptive traits.[25]

Consequently, the terms "disorder," "randomness," "irregularity," "lack of symmetry" would seem to imply the lack of repetitivity within a heterogeneous pattern of the object described.[26]

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[25] "What is logically prior to relationship is difference and similarity, leading to order" (Bohm, 1969/21).

[26] Although Popper (1972/359) does not use the word "repetitivity," he discusses the possibility of defining the objective disorder (randomness) in terms of the "absence of regularity." He rejects this definition for the reasons which might be valid in the domain of pure formal logic, but do not seem convincing in the context of physical and biological phenomena. His first reason seems to be the practical incapacity to decide whether an apparently non-repetitive (random) pattern is not repetitive upon a higher level of the observational scale range. This difficulty, however, does not exclude the possibility of the final and certain recognition of the order (repetitivity) upon the actually observed scale range. In this way, a certain epistemological assymmetry between the observational order and disorder would appear, and that might also influence Popper's refusal to identify the order with repetitivity, and the disorder with the lack of repetitivity.

The above confrontation of terms and the corresponding ideas have some important consequences for the interpretation of the way in which the characteristic phenomena of life are described.

1.11 The notion of order and the notion of redundancy

First, confrontation reveals a strange lack of consistency in the notion of "information" as accepted by "information theory." If "the entropy of a system is a measure of its degree of disorder" (Uvarov et al. 1971/ 134)[27] it is translatable into an "information" quantity (see Conrad 1970/195) and at the same time the term "redundancy" means that the value of "information" is less than maximum, the"ordered," "regular," "symmetrical" systems (objects) will be redundant in terms of "information theory." If, then, a living organism produces an (observational) order out of disordered environmental elements (Hotchkiss 1958/145), the information within the system (environment-organism) decreases rather than increases.[28] Bohm (1969/29ff.) has pointed out these contradictions involved in the notion of entropy, but unfortunately, he seems to use the term "order" in a double sense. First, he uses it in the sense in which order is opposed to randomness, and secondly, in the sense in which a more heterogeneous (complex, and possibly random) system is of higher "order" than that which is less heterogeneous. The origin of the above-described contradiction, or at least confusion, has been analyzed by Mor-owitz, who pointed out how some terminological ambiguities may lead to the identification of the increase of information both with the increase of entropy and with the negentropy (entropy decrease) as well (1971/108). The confusion originates because the term information is carelessly used sometimes to denote our actual knowledge about the microstate of the system and sometimes to denote "the amount of residual ignorance we have about the microstate of the system"

[27] "The notion of entropy is inseparable from that of probability, which is in turn inseparable from that of randomness" (Bohm, 1969/29).

[28] Waddington (1968/8-9) discussed inapplicability of the "information theory" to the biological (and in particular to hereditary) phenomena. He too points out quite explicitly that the word "information" means nothing more than "amount of variety" (we might say the "amount of heterogeneity").

(1971/106). Blandino (1969/276ff.) is also aware of the ambiguity involved in the thermodynamic speculations on the nature of life. He expressly states that:

> "the morphologico-functional order does not coincide with that (anti-en-tropic) order which diminishes whenever entropy increases...biological order may, within most ample limits, be increased both when the anti-entropic order increases and when it diminishes, and vice-versa."

He quotes in this context Lwoff (1960), who has made a similar observation.

Secondly, the intrinsic heterogeneity being a necessary but not a sufficient condition of observational order, the observational order registered in the living world creates two distinct, separate and independent questions:

a) How is an increase of heterogeneity effected?
b) How is the repetitivity of this heterogeneity produced?

Let us imagine a number of polypeptides in a solution, and let us assume that each one of them is different (is constituted by different sequences of 20 basic aminoacids). The solution is then absolutely heterogeneous in terms of this observational scale range upon which separate polypeptides dan be recognized and their structure compared. If now we will add to the solution the set of proteolytic enzymes, all our polypeptides will be decomposed into single am-inoacid molecules. Fran these aminoacid molecules the new polypeptides might be constructed, this time identical ones. Any polypeptide is more heterogeneous than a single aminoacid. Some polypeptides may be identical, some others may not. It is another problem to explain how aminoacids are linked together in *a* heterogeneous structure of a polypeptide, and another to explain how it happened that all the newly formed polypeptides are alike (why their pattern is repetitive).

1.12 The changes in the order, homogeneity and heterogeneity Summing up the above discussion we may say that:

1. The order within an object under observation is recognizable when ever a heterogeneity of the descriptive pattern and the repetitiv ity of this pattern is observed.
2. The repetitivity of the heterogeneous pattern within an ordered system should be distinguished from the identity of descriptive traits within an observationally homogeneous object.
3. In order to judge whether we are concerned with an increase (or decrease) of order, the following observational elements should

be taken into account:

10. The overall heterogeneity of the observed pattern which may suitably expressed in terms of "information theory."

11. The eventual differences between the observational scale range upon which the observational traits of the compared objects were regis tered.

12.The relationship between the repetitive (ordered) and non-repetitive (random) element of the heterogeneous patterns in both cases.

An increase of heterogeneity may happen in a double way:

10.a regular pattern may be transformed into an irregular, random pattei

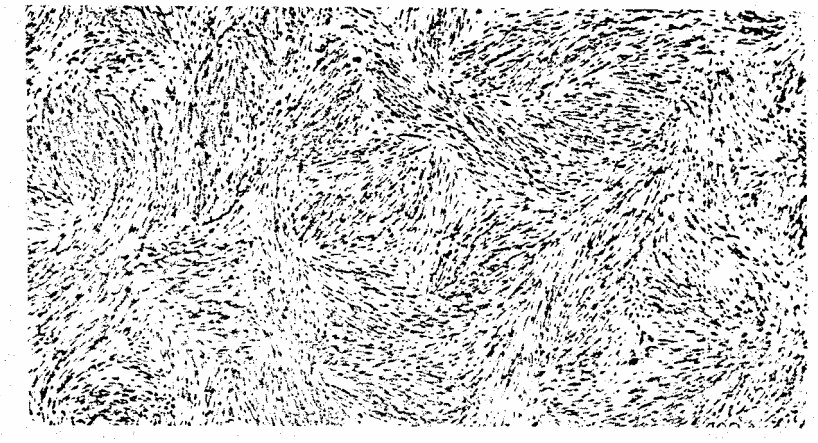
11. a higher level (in the sense of the higher observational scale) of heterogeneity may be formed.

Similarly, an increase of order may be effected in a double way:

10. a random pattern may be made non-random (as, for instance, happens in the case of crystallization of a substance in a solution).

11. the heterogeneity of the system may be "lifted" upon the higher level of organization, and then a repetitive pattern may appear on this higher level. (That is the case of in vivo protein synthesis, during which the inorganic compounds are linked together into complex struc tures, and these complex structures are observed to be *identical*, i.e. repetitive).

Fig. 1.1 Observational,descriptive notion of order (repetitivity) and the notion of random. "Three days after random initiation... the arrangement of the cells (monolayer culture of human fibroblasts) is no longer random. The cells form ... parallel arrays termed groups. It is groups that lie at random rather then the cells. (Elsdale 1972, Fig.l)



The above changes in heterogeneity and/or order have to be distinguished from the changes in the observational homogeneity. This may happen in two ways:

1. If the repetitivity of pattern (order) increases, (and, consequently, the randomness decreases), the obj ect may (upon a certain observation al scale range) appear as more homogeneous than before.
2. An object may undergo "randomization" (natural or artificial) during which the dimensions of its details become smaller, and consequently they may cease to be recognizable as different within a given ob servational scale range.

In both cases, randomness of the object decreases, while in the second case the order may decrease too.

1.13 The distinction between the observational notion of order and the aausa.1 notion of order

The notion of the observational order should be carefully distinguished from the notion of the causal order. The observational order has to be recognized in any object which manifests repetitivity of heterogeneous pattern. But the repetitivity of heterogeneous pattern may appear as a result of random causal influences or as a result of ordered causal influences. Similarly, observational homogeneity (or observational heterogeneity) may result from random influences or, to the contrary, from integrated influences. The homogenization of the food during the digestive, mechanical and chemical processes in the stomach results undoubtedly from the integrated physiological function of the digestive system, while the decay of a dead body results from completely independent environmental random influences.

The repetitive pattern of crystal structures does not arise from an integrated causal influence, but the repetitive structure of protein functional molecules (hemoglobin, myoglobin, insulin...etc.) observed in the living body presupposes the existence of an integrated (non-random) synthetic mechanism. Why is this so? What sort of criteria decide about the different causal explanation of different forms of order? These questions constitute the main theoretical problem involved in the notion of phenotype-genotype dichotomy.

CHAPTER TWO

THE HISTORICAL INTRODUCTION TO THE OBJECT OF STUDY

2.1 *The double origin of the "phenotype-genotype" conceptual framework*

The modern meaning of the "phenotype-genotype" conceptual scheme is the product of a complex evolution which started at least a hundred years ago and was determined by two different currents of biological observation, experimentation and interpretation.

One of these currents was investigating remote origins of differences observed between groups of organisms (theory of evolution) and actual transmission of some differences between parental and offspring organisms (horticulture and breeding)[29] (Sturtevant 1965, Ravin 1969, Sentis 1970).

The second current was concentrating upon the phenomenon of repetitively appearing structures of an organism's body. These structures were apparently growing "de novo" from such relatively simple objects as eggs, pollen ... and the like. Embryologists and pathologists, on one hand, and morpholo-gists and physiologists, on the other, were particularly interested in this phenomenon commonly referred to as "epigenesis" (Hughes 1959; Hall 1959, II; Stubbe 1972).

Although the phenomenon of the "de novo" formation constituted to a certain extent the common element in both currents of biological progress, the differences between them were nonetheless quite significant. One current put stress upon the differences, while the other stressed the identical traits. Consequently, the first current was concerned about the relationships between different species and different individual organisms, while the second was mainly absorbed in the redescription of those relationships which exist (or arise) between the parts of the same individual. In both cases the descriptive methodology and the speculative elaboration of the results were necessarily different. At this point we need to see how the "phenotype-genotype" dichotomy was formulated by the representatives of the two approaches, and how the modern concept

of the phenotype-genotype dichotomy is affected by its double origin.

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[29] "The name Genetics was given to this branch of biology by Bateson in 1906 in an address to the Third Conference on Hybridization and Plant Breeding... In his address Bateson said: 'I suggest for the consideration of this congress the term Genetics, which sufficiently indicates that our labours are devoted to the elucidation of the phenomena of heredity and variation: in other words to the physiology of descent, with implied bearing on the theoretical problems of the evolutionist and the systematist, and application to the practical problems of the breeder, whether of animals or of plants'" (Levine 1971/92).

For the sake of clarity, we will refer to the first investigational approach as "Mendelian" genetics, while we will refer to the embryological and physiological approach as "Weismannian."

2.2 *"Mendelian" genetics*

According to Dunn:..."The first source of interest in question of heredity and variation, which led to modern genetics, came from agricultural pursuits such as animal and plant breeding, horticulture and gardening...(1969/ 4). What were the most important concerns for the breeder or the horticulturist? It was the process by which some selected, peculiar traits of a plant or an animal are transmitted. The Greeks were already interested in the hereditabilty of such traits as "peculiarities of hair and nails, and even the gait and other habits of movements" (Sturtevant 1965/1). Mendel writes:

> "Numerous experiments have shown that if two plants differing in one or more characters be crossed with each other, the common characters will be transmitted without change to their hybrid progeny, but that each pair of different characters will, on the other hand, combine together to form a new and usually variable character in the offspring. The object of my experiments was to observe such variations in connection with pairs of different characters and to deduce the laws governing their appearance in succeeding generations" (1865/57ff.).

Mendel obviously did not concentrate his attention upon the "common characters transmitted without change" but on those characters which make the difference between two living bodies or two groups of living bodies. It was not the stability of the bodily structure and frunction which constituted the main object of his study but its variability. The unity of the whole plant was, of course, not questioned, but simply passed by. A character, selected by comparing two different individuals, was what intrigued him. He discovered that the characters he selected for study "do not mingle, but maintain their particular quality without blending with the characters imparted by the other parent" (1865/ 90). In this way the concept of a character as a unit was born. A good experimentalist and observer, Mendel realized the complete lack of proportion between the descriptive qualities and the apparent homogeneity of the pollen which was sufficient to fertilize his hybrid plant and the fully developed and variegated "unit-characters." As a result, he postulated the existence of "factors" which determined the re-appearance of the given trait in the offspring. The concept of "factor," although not elaborated during the first period of classical genetics, introduced a sort of dichotomy between the material inherited from the parent organism (a set of "factors") and the observable characteristics of the

adult offspring. This somewhat mysterious "factor" makes, in Whitehouse's opinion (1970/12), the "fundamental difference" between the Hippocratic or even Darwin's theories of heredity and the theory of Mendel.

> "Mendel postulated the units of heredity that we now call genes. He did not know they were in the nucleus of the cell or that they were carried in chromosomes. But he did know that they determine whether pea seeds will be round or wrinkled, whether green or yellow, whether the flowers will be purple or white, whether the pea plant will be tall or short, and so on. He had a remarkable understanding about how genes are transmitted from one generation to the next" (Beadle, 1961/511ff.).

In 1900 the unnoticed results and interpretations of Mendel were re-discovered by De Vries, by Correns and by von Tschermak, the people who were also selectively interested in the phenomena of plant variability. This focusing of the attention on the "specific characters" of an organism might be well illustrated by the following text:

> "the specific characters of organisms are composed of the separate units. One is able to study experimentally these units by the phenomena of variability and mutability or by the production of hybrids. In the latter case one chooses in preference hybrids from parents which are distinguishable from each other by only a single character or by a small number of well-defined characters and for which one considers only one or two of the units and leaves the others aside ..." (De Vries, 1900.)

The term "specific," i.e., distinguishing, individualizing, does not necessarily refer to any of the structural and/or dynamic properties of the organism which are biologically (physiologically, functionally, developmentally) relevant but only those which are easily traceable in terms of the differences and do not affect the proper functioning of the body as a whole.

As we have said, Mendel deliberately disregarded the possible functional meaning of his "characteristics." The "roundness" and "wrinkledness," "colorness" and "whiteness" are certainly not the only observable properties of tne living organisms. It is also not quite certain whether the "tallness" and "shortness" or "greenness" and "yellowness" are really so sharply distinguished one from another, but, as Waddington writes: "Mendel was bold.enough to leave out of the consideration the greater part of the characteristics of the organisms with which he was Vorking and to concentrate on one or two sharply marked features" (1939/30). The main result of Mendel's experiments was the realization that his "characteristics", behaved as completely independent units of heredity, and that their "sorting" between the two successive members of offspring generation followed in surprisingly precise manner the methematical formula of purely random distribution (Cfr. Whitehouse, 1970/27).

In such a way, at the very beginning of Mendelian genetics, the concept of the "unit" of heredity and the concept.of randomness (see Correns 1900/ 158-168) entered into the field of biological investigation.[30]

From the epistemological point of view, it is worth mentioning that the conclusion about the independence of transmitted "factors" was drawn from the observation of the random pattern in which the "characters" were reappearing in the successive generations, and not vice versa. Randomness of a heterogeneous pattern is thus an observational manifestation of the causal heterogeneity and the mutual independence of the causal factors.

This early conclusion of Mendelian genetics was considerably modified by forthcoming new evidence.[31] The distinction between the "factor" and the observable character, however, has remained valid. We will recognize this distinction in the dichotomy between the "phenotypic" and "genotypic" reality.

2.3 "Weismannian" genetics

> "We must remember that the concept of heredity had a meaning in ancient times quite different from that which it has today. Heredity simply meant the procreation of offspring of the same kind with the same or similar features...The concept of heredity included, in the first instance, the totality of physical and mental characters and features (Italics PL's). It was only with Hippocrates, Aristotle, and others after them that the inheritance of specific characteristics, deformities, and illnesses was envisaged" (Stubbe 1972/12).

In modern times this "holistic" approach towards the problem of heredity may be best illustrated by the following texts:

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[30] Discussing philosophical background of physical atomism, Whyte states: "If there really exist ultimate units, we have only to discover their laws and all their possible combinations, and we shall be all-knowing and all-powerful, like gods —" Pointing out that Brownian motions constitute probably "the most striking direct evidence of discrete structures,"(randomness of Brownian motions implies independence of particles), Whyte continues: "Agnosticism could do no serious harm to religion as long as it continued to believe in order, but agnosticism based on atomic disorder was not merely an anti-Christian rebellion; it was an organized assault on all the gods, on the very idea of God, on Order itself..." (1961/15, 17). Mendel's observations constituted the first direct evidence for random processes in the realm of biological non-pathological phenomena.

[31] "The triumph of classical genetics came not from the monotonous confirmation of Mendel's postulates...but rather from an astonishing series of complications and contradictions [the new observations] revealed—how complex the genetic machinery was in living things, how lucky Mendel was to investigate uncomplicated character differences in the pea plant, and how wise he was to exploit what he had, for as in all scientific progress, it is more likely that complicated truth will evolve from simplified, first approximations than simple truth from complicated hypotheses..." (Ravin, 1965/10, 15; see also Fruton 1972/233).

> "When we see that, in the higher organisms, the smallest structural details, and the most minute peculiarities of bodily and mental disposition, are transmitted from one generation to another; when we find in all species of plants and animals a thousand characteristic peculiarities of structure continued unchanged through long series of generations —we very naturally ask for the causes of such a striking phenomenon" (Weismann, 1885).[32]

> "That a [germ] cell can carry with it the sum total of the heritage of the species, that it can in the course of a few days or weeks give rise to a mollusk or a man, is the greatest marvel of biological science" (Wilson, 1900).[33]

The above texts stress the problem which arises because of the repetitivity of the overall structural and behavioural pattern observed in every new generation.

This question arose in the nineteenth century because of the fall of the previously prevailing theory of preformation (See Coleman 1971/33) and the final victory of the observational evidence over the speculative prejudices.[34] The preformation theory, in its most extreme form, simply denied the reality of the developmental processes in the embryo[35] and claimed that the epigenetic process is unthinkable and impossible.[36]

It might be quite interesting to investigate how the theory of preformation with all its rather incredible consequences (Mason 1953/292; Jacob 1970/63ff.; Stubbe 1972/83) survived so many years and, indeed, how it started at all.[37] The epigenetic phenomena of development were always

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[32] Quoted after Moore, 1972/56-7.

[33] Ibid., 1972/79.

[34] C. Bonnet considered the preformation theory as "one of the greatest triumphs of the rational over sensual conviction" (quoted by Oppenheimer, 1966/ 130).

[35] "Qui igitur systemata predelineationis [i.e., preformation - PL] tradunt, generationem non explicant, sed, eam non dari, affirmant" (Cf. Wolff, quoted by Oppenheimer, 1966/132-3).

[36] Cfr. Hall, 1969, 11/37. Woodger (1967/371) quotes Wilson who wrote that: "Fundamentally epigenesis is inconceivable [because] we are unable to conceive how a self-determining system can increase its own initial complexity."

[37] Needham in his "History of Embryology" (1959) provides us with some details of the observational background upon which the preformation theory was built.

macroscopically observable. Coiter's careful and detailed study on the chicken's development was published in 1572,[38] a hundred years before Malpighi generalized his erroneous interpretations of the data concerning the blastoderm tissue.

However, in the early nineteenth century, the macro- and microscopic evidence was clear enough to remove any rational doubt on the true course of events during the development of the metazoan organisms. The descriptive concept of the "de novo" formation of tissues and organs provoked a certain mental crisis which was eventually solved by splitting the idea of the organism into two parts. One was the changing and developing "soma," and the other the preformed, stable "hereditary material."

The above distinction was stated in different ways by several other nineteenth century biologists.

> "Periodicity with which successive generations of life move from simplicity to complexity" (Hall 1969 II/325)

intrigued Haeckel and von Nageli who postulated a distinction between the passive "trophoplasm" and the active "idioplasm."[39] These ideas were later developed in some detail by Weismann, who stated clearly the difference between the body ("soma") and its "germ-plasm" which gradually confers to the developing body its unity and intrinsic organization.[40] We can see that, unlike the Mendelian concept of the "gene," the Weismannian concept of "hereditary material" was provoked by embryological observations and by phenomena immanent to the body itself. This body was considered here as an integrated whole and as a dynamic phenomenon.

2.4 The comparison of "Mendelian" and "Weismannian" approach to the phenomena of heredity

We will now compare the "Mendelian" dichotomy between "factor" and "character" or "trait," on one hand, and the "Weismannian" dichotomy between "germ plasm" and the "soma," on the other. We will note the following similar-

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[38] Coiter's study, "De ovorum gallinaceorum generationis primo exordio progressuque et pulii gallinacei creationis ordine," was translated and published by Hall in 1971.

[39] "The idioplasm acts molecularly to control the inner structure, outer form and function of neighboring non-idioplasmic material and in this way all the important properties of the plant or animal" (Hall, 1969, II/336).

[40] Cfr. Weismann's essay, "The Continuity of the Germ Plasm as the Foundation of a Theory of Heredity," published in 1885. English translation in 1891-92, abridged and published by Moore, 1972/56ff.

ities and differences.

a) In both cases there is a distinction between something which is directly observable and something which is postulated as an explanatory, causal agent.

b) The major difference between "Mendelian" and "Weismannian" approach seems to be this. Using Bohm's terminology, the "Mendelian" approach concentrates its attention upon the "distinctive differences," while the "Weismannian" approach concentrates upon the "constitutive differences."[41]

c) The material provided by the parent organism does not reveal the "constitutive" or the "distinctive" differences. The offspring adult body manifests both. In both the "Mendelian" and the "Weismannian" approach, the "question-raising" evidence seems to consist in the "de novo" appearance of the (relative) heterogeneity from the (relative) homogeneity.

d) "Mendelian" traits are randomly distributed among progeny, while the "Weismannian" characteristics re-appear in a non-random pattern. In the former case the causal agency is postulated to explain random epigenesis, while in the latter, it is invoked as a postulatory causal agent producing an ordered epigenesis phenomena (See Fig. 2.1).

Now, we will see how these two interpretative approaches meet and converge in the contemporarily accepted terminology.

2.5 The origins of modern terminology — the concept of phenotype

In 1909 Johannsen coined the terms "phenotype" and "genotype" to denote presumably distinct realities, and his terminology substituted in modern texts the original terminology of early geneticists.[42]

The term "phenotype" denotes the primary observational evidence and the term "genotype" denotes the postulatory factor, the causal entity which for a considerable period of time remained unidentified so that its real existence has often been put in doubt.[43]

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[41] "Constitutive differences" determine the essence of the order of whatever we are talking about. "Distinctive differences" determine how one type of order can be distinguished from another (Bohm, 1969/21).

[42] On "gemmules" of Darwin, "physiological units" of Spencer, "Bioblasts" of Altmann, "plasmosomes" of Wiesner, "idioblasts" of Hertwig, "idioplasm" of Nageli, "ids" of Weismann, "Biogens" of Vervorn, see Hall (1969, II/334ff.).

[43] "No definite idea about the nature of the "genes" is at present sufficiently well-grounded" (Johannsen, 1909, p. 124-5, cited by Fruton, 1972, p. 240). Although Johannsen writes: "that 'gene'...may be tentatively considered to be chemical factors of various kinds" (ibid.), "the concept of gene had remained largely devoid of any material content for the fifty years following the rediscovery of Mendel's work" (Stent, 1970, cited after Moore, 1972, p. 253; cfr. also Muller, 1947). These quotations have to underline the postulatory, speculative meaning of the concept of gene (genotype) but the nature and the origins of the concept will be analyzed in the latter part of our study.

Johannsen's definition stresses the observability of the phenotype:

> "I have designated a statistical, i.e., purely descriptively established type, as an 'appearance type' (Erscheinungstypus), a phenotype. Phenotypes are measurable realities, just what can be observed as characteristic, in variation distributions of the 'typical' measurement, the center around which the variants group themselves."[44]

The terms "typical" or "characteristic" might suggest that the term phenotype includes only the descriptive characters common to a group of entities. But Johannsen writes:

> "The word phenotype, however, finds its use not merely in statistically ascertained 'typical' averages but can without addition be used to designate the personal peculiarities of any individual whatever."[16]

It might seem that the phenotype in its original sense applies only to the abstract (that is, mentally separated from their context) "traits," or "characteristics." But it is not so:

> "The phenotype of an individual is...the sum total of all of his expressed characters. The single organism, the individual plant, and animal, a man. 'What he is and what he does'.. .[16]

Johannsen put such a stress upon the observability of the phenotype that he didn't even want to include in his concepts the distinction between the living and non-living world:

> "Through the term phenotype the necessary reservation is made, that the appearance itself permits no further conclusion to be drawn. A given phenotype may be the expression of a biological unit, but it does not need to be."[16]

This all-inclusive meaning of the term phenotype is still recognized in the definitions we find in modern textbooks on genetics. Some definitions taken literally might suggest that any physical entity has its phenotype:

Phenotypes are "easily distinguishable external characteriscits" (Mahler and Cordes, 1971/844);

"The classifications which we make by means of our senses are known as phenotypes" (Snyder, 1957/18);

"The property of an enzyme is in fact part of the molecular phenotype" (Goodwin, 1970/5).

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[44] Johannsen 1909, a,162-3, cited after Dunn 1965, p. 91.

But the usual meaning of this term is restricted to the content of the living-world phenomena. And it is tacitly assumed that "roundness" or "whiteness" of a cloud or a given length of a stone are not phenotypes, in spite of their observability. During the last half century, the original sense of the term phenotype was gradually restricted. Now it is closer to the concept of the "hereditary trait." We will discuss the relationships between these two concepts in the latter part of our analysis.

The term phenotype can still be used to denote a given observational detail of the living body:

> "Phenotype is the 'appearance of an organism with respect to a particular character or group of characters' (See, e.g., Gray, 1967; Carlson, 1967/157; Whitehouse, 1970/389; Hawker and Linton, 1971/99).

It can also refer to the whole observational evidence concerning a given living body:

> [Phenotype is] "the sum total of all characteristics, such as color, form, size, behavior, chemical composition and structure, both external and internal, gross and microscopic ...The phenotype of an individual changes with time, as illustrated, for example, by a series of photographs of a person taken at different ages from infancy to senility. But we also know that the more subtle physiological changes constantly occur in an individual, so that the phenotype is never exactly the same from one moment to the next...We recognize persons or individuals of any species of animal, or plant, by their phenotypes..." (Sinott et al, 1958/18)

Rieger et al. (1968) have stated expressly that the term phenotype can be applied either to particular characters, traits or phenes or to their totality. We may conclude then that the term "phenotype" according • to the context in which it appears may be interpreted either in the sense of a "Mendelian" detail or a "Weismannian" whole.

2.6 The origins of modern terminology — the concept of genotype

Carlson reconstructs the speculative origins of the term and the concept "gene" (genotype) in the following way:

> Mendel called his traits "characters" and the biological basis for these characters was attributed to internal "elements"—Johannsen introduced the term "gene" as a replacement for...Mendel's hereditary "elements." Johannsen did not define the gene; he couldn't. He merely said it was convenient to have a word for the "something" in reproductive cells that eventually led to traits ... he suggested the term "phenotype" for what the geneticists saw...(1967/1-2).

The "convenience" of having a word for "something" which "led" to traits manifests the epistemological impossibility of reducing the reappearance pattern of the traits to the sole re-description of this pattern. In other words, the

observationally registered "re-appearance pattern" is obviously considered causally irreducible to itself!

The clear recognition of the difference between a re-description of the details of a process and the discovery of the nature, principle or essential agent which determines the process as a whole may be illustrated by the following text:

> "We have no glimmering of an idea as to what constitutes the essential process by which the likeness of the parent is transmitted to the offspring. We can study the process of fertilization and development in the finest detail which the microscope manifests to us, and we may fairly say that we have now a thorough grasp of the visible phenomena; but of the nature of the physical basis of heredity we have no conception at all. No one has yet any suggestion, any working hypothesis, or mental picture that has thus far helped in the slightest degree to penetrate beyond what we see. We do now know what is the essential agent in the tranmission of parental characters, nor even whether it is a material agent or not? (Bateson, in Carlson 1966, p. 5-6).

The details of fertilization and development constitute an observational event, an observational fact which raises the question: "What is the nature of this process?" or "What agent is responsible for this process?" This question cannot be answered by a repetition of the facts which have raised it. "Something" else is to be postulated to explain causally this reappearance pattern. As we have seen in the preceding discussion of the phenotypic phenomena, the epigenetic, *de novo* formation of traits together with its repetitivity, constitutes the essential (abstract) element which provokes this epistemological attitude.

An unknown, postulatory element of living body "functions" (Yost, 1971) "causes" (Ruse, 1973), "operates" (Hamburgh, 1971), "determines" (Horowitz, 1956; Rieger et al., 1968, Whitehouse, 1971; Russell, 1930), "controls" (Beadle and Tatum, 1941; Whitehouse, 1971; Yost, 1972), "guides" (Beadle, 1948; J. H. Muller, 1965), "governs" (Monod and Jacob, 1961) the re-appearance of the phenotypic traits, both in the sense of the separate units and in the sense of the whole, integrated phenomenon.

This postulatory causal agency may be conceived either in the "Mendelian" analytic way or in the more integrated "Weismannian" way.

The "Mendelian" idea of phenotype conceived as a set of independently hereditable characters, reflected upon the "Mendelian" idea of postulatory causal agency. This agency was conceived here as a set of independent "genes," the set being called collectively the "genotype." The "Mendelian" genotype denotes the sum total of genes carried by a single gamete. Because the single "pheno typic"

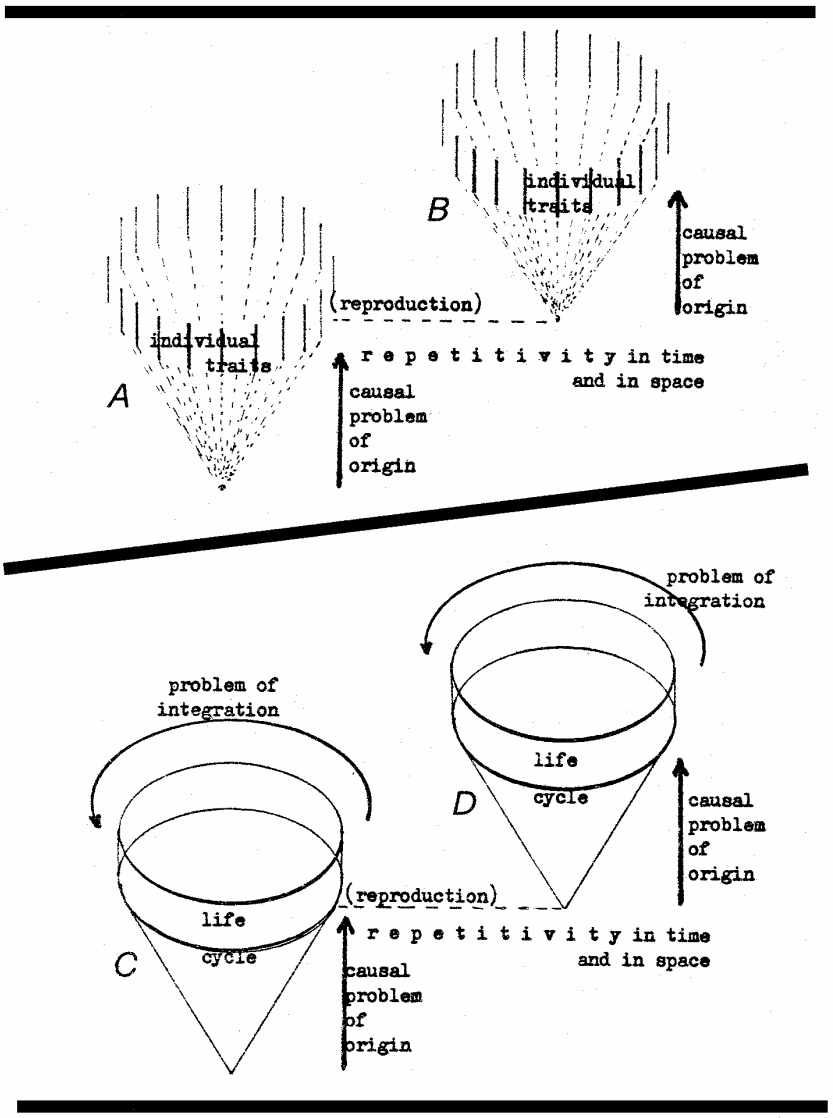

Fig.2.1 Differences between "Mendelian" genetics and "the Weismannian" genetics.

A,B -"Mendelian" observational approach

C,D – "Weismannian" observational approach

traits are transmitted independently, no intrinsic integration is postulated within the set of genes. This extreme position is no longer held by the majority of geneticists, although it survived, to a certain degree, in population genetics.[45]

What is the difference between the concept of the "gene" and the concept of the "genotype" or the "genome"?[46] The gene is supposedly an indivisible (smallest) entity which can still be considered as "hereditary material" or a "hereditary determinant." The genotype'(or the genome) denotes the sum total, the entire genetic constitution of a single organism, the assortment of genes of an individual, all the genes carried by a single gamete. In a way, the genotype is rather a Weismannian concept, while the gene is a Mendelian one. Still, neither of them is predetermining the further interpretation. The concept of the gene as such does not exclude a more integrated, non-random organization of the hereditary material taken as a whole. The concept of the genotype does not exclude the possibility that its parts are relatively independent one from the other.

In each case the concept of the hereditary material serves as a causal explanation for the epigenetic phenomenon. Identification of the hereditary material, or, in modern terms, of the genotype will mean identification of the cause of life phenomena. We know that during the last decade, the genotype was identified with the nucleic acids present in the cell. In the later part of our study, we will try to answer the question of the essential properties of epigenetic phenomena, as manifested on the elementary level of life. There we will try to grasp the meaning of this question-raising evidence. This will enable us to state the criteria for the identification of the genotype's agency and to determine to what extent these criteria are fulfilled in the case of the nucleic acids.

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[45] „Population geneticists are aften accused of having failed to incorporate the findings of modern molecular genetics. But the situation is far worse than that … Nearly the entire corpus of literature in theoretical population is written from the standpoint of single Mendelian genes, or else genes that all obeyed the law of independent segregation" (Lewontin, 1970/63).

[46] In 1920, Winkler introduced the term „genome" to denote the *total* genetic information. While the term „genotype" is used nowadays both in the sense of the total genetic information and in the sense of a part of it, the term „genome" is used rather exclusively to denote the *total* genotype. The usage of these terms is not, however, consistent, and only the broader context in which they appear determines how the should be understood.

From the methodological point of view, we will try not to exceed the limits of these concepts which are already present in the minds of contemporary biologists, and at the same time to put the stress upon the logical consequences of them. In this way, we hope, philosophical analysis will make more explicit that which was considered "essential" by the biologists themselves, and at the same time show the speculative "workshop" of modern biology as used in a concrete field of empirical study.

CHAPTER THREE

PHENOMENA OF LIFE -- REPETITIVE EPIGENESIS

In the preceding, historical part of our essay, we have tried to analyze the most rudimentary background of the distinction between these elements of the science of heredity which are believed to constitute the "question-raising" evidence of this science (the phenotype), on the one hand, and the idea about the "question-solving" reality {the genotype), on the other.

In this part of our study we will investigate some concrete data concerning the actual manifestations of life. This will lead us to a deeper understanding of the essential elements which characterize the question-raising element of genetic theories.

This investigation will be carried out in two steps.

First, the hereditary characteristics of an organism will' be distinguished from the non-hereditary ones, and their common empirical properties will be analyzed, abstracted and generalized. This will lead us to a realization as to why the phenomenon of repetitivity and the phenomenon of increase in heterogeneity constitute something to be explained by an appropriate causal theory.

Secondly, the phenomenon of integration which pervades basic phenomena of heredity will be analyzed, abstracted and defined. This will help us in a fuller understanding of sane necessary postulates which have to be included in the causal theory.

The first step will thus lead us to the concept of repetitive epi-genesis, the second to the concept of integrated epigenesis. The repetitivity and integration will constitute, as we will see, the main question-raising observational properties of these epigenetic phenomena which are registered within the sphere of living organisms.

3.1 The distinction between the hereditary and non-hereditary trait

We have to analyze once again the notion of heredity, this time the modern one. This should reveal the basic premises of this notion and realize the essence of the distinction between the hereditary phenomena as opposed to the non-hereditary ones. Being conscious of the two different approaches we discussed in the previous chapter, we will approach the analysis of hereditary traits from two extremes. We will analyze the hereditary trait in its

"Weismannian" holistic aspect and in its "Mendelian" analytic aspect. We will see that in both cases the idea of repetitive epigenesis comes out very clearly.

"Mendelian" genetics is founded upon the distinction between hereditary and non-hereditary (acquired) traits. The origin of non-hereditary (acquired) traits is reducible to the environmental influences, or in other words, to the purely physico-chemical causality of the inanimate world. Acquired characters are "produced by influences originating outside the organism" (Borland's Medical Dictionary, 1974); they are defined as "phenotypic modifications arising purely by environmental influences during the developmental process of an organism."(Rieger et al. 1968/55). The notion of acquired characters helps us to understand what is the more exact meaning of the causal reducibility in genetics and to discover these elements of hereditary traits which prevent us from reducing their origin to the environmental influences.

It is obvious that the idea of causal irreducibility is to be hidden somewhere in the criteria which are used to distinguish the non-hereditary (acquired) traits from the hereditary ones. So we have to consider the definition of hereditary trait.

3.2 Definition of the hereditary trait

The notion of the hereditary trait is opposed to that of the acquired trait. Both traits belong to the sphere of phenotypic phenomena. The criteria of the distinction between them make reference to the phenomena of reproduction, on the one hand, and to the notion of "environmental influences," on the other (Rieger et al., 1968/55). This may he well illustrated by the following definition: hereditary trait:

1) "appears in successive generations"

2) "does not fluctuate in response to environmental changes" (Baer et al., 1971/138)

It seems, then, that the definition of the hereditary trait, its recognition, is dependent upon earlier observational and interpretational steps, namely:

a) recognition of a group of living bodies tied together by the link of reproduction phenomena;

b) recognition of the difference between a living body and its surroundings.

The first premise puts forward the problem of the non-arbitrary delimitation of the basic entitative unit of life, an organism. Without this

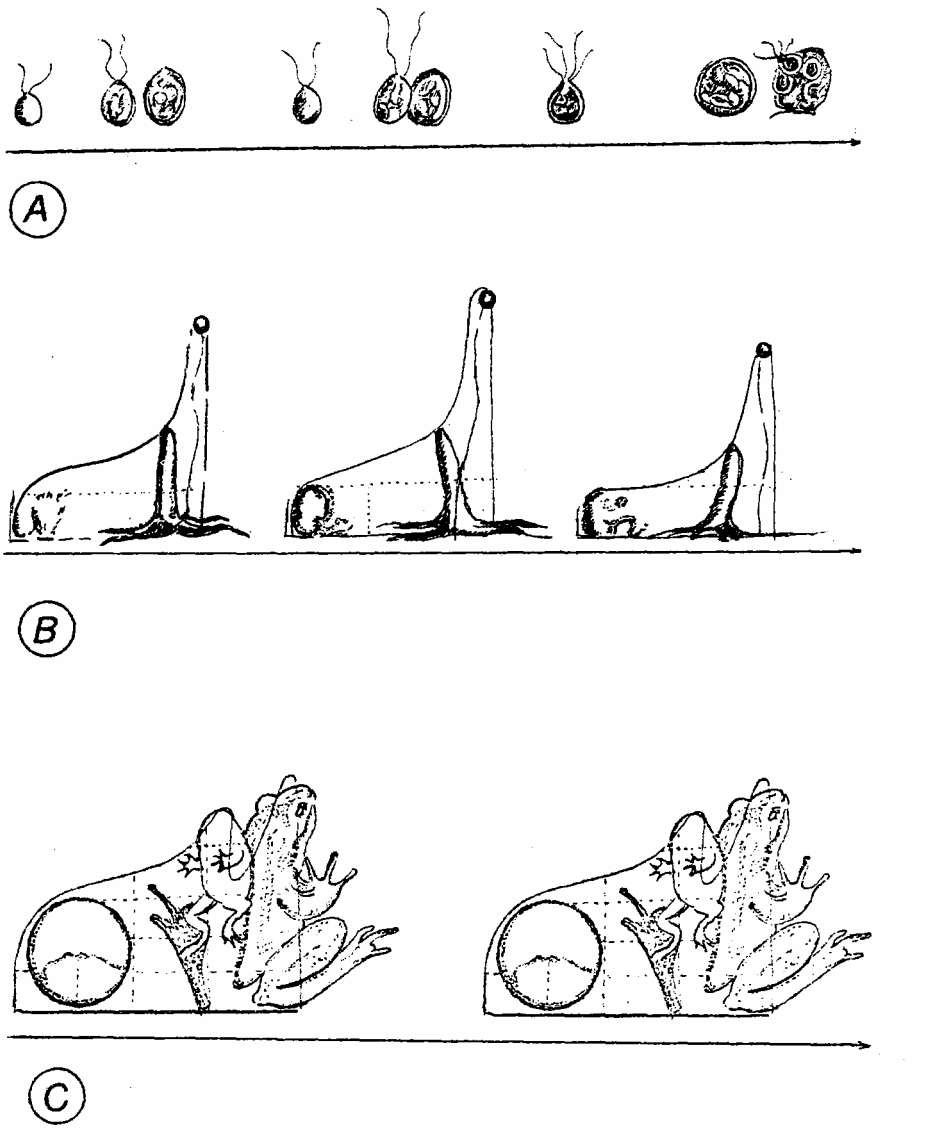

Fig. 3.1 Life cycles of: A. - Alga *Chlamydomonas Reinhardi,* B. - Slime mould *Dictyostelium mucroidea,* C. - frog *Rana pipiens.*(After Booner 1965,plates 3,6 and 25)

delimitation the notion of "generations" makes no sense.

The second premise forces us to reflect upon the way in which the selection of traits for genetic study is made and to a deeper reflection upon the non-arbitrary means of distinguishing between the organism and its surroundings.

Let us then consider the concept of organism, as presupposed by the elementary genetic ideas.

3.3 The basic unit of heredity — life cycle

The life-span of any living form is limited. Its maximum length, in time dimension, is species specific and hardly modifiable by external factors. The prolonged existence of life phenomena is thus possible because of the succession of generations. The continuity of life is not a steady state but a periodic fluctuation between a structural minimum, in terms of heterogeneity, and a maximum. The single periods are recognized because of the repetitivity of their observational properties, upon any observational scale range, and are commonly referred to as "life cycles." Within a single period, heterogeneity (assymmetry) of events, analyzed along the time vector, is, on the whole, absolute.

The continuity of periods might be illustrated by the following examples:

a) frog...egg...tadpole...frog...egg...tadpole...frog...egg...

b) one cell...two cells...one cell...two cells...one cell...two...

c) seed...tree...seed …tree...seed...tree...seed...tree... (See Fig. 3.1 and 3.2)

Theoretically, the division, which is purely mental, between the periods may be made at any arbitrarily selected point along the time vector. It might be put between the egg and the tadpole, or between the tadpole and the frog, but in each case the phenomenon of repetitivity would be saved. Each element arbitrarily selected along the time vector reveals its particularity, and each one of them reappears in due time. We may ask, then, whether the continuity of the periodicity is absolute or not. The absolute continuity would mean that a separation of one period from another is always arbitrary, independently of the point at which the division line was drawn. If, on the other hand, it were possible to recognize such points which manifest an intrinsic property distinguishing them from all the other points, we might say that the continuity of periods is not absolute, but only relative.

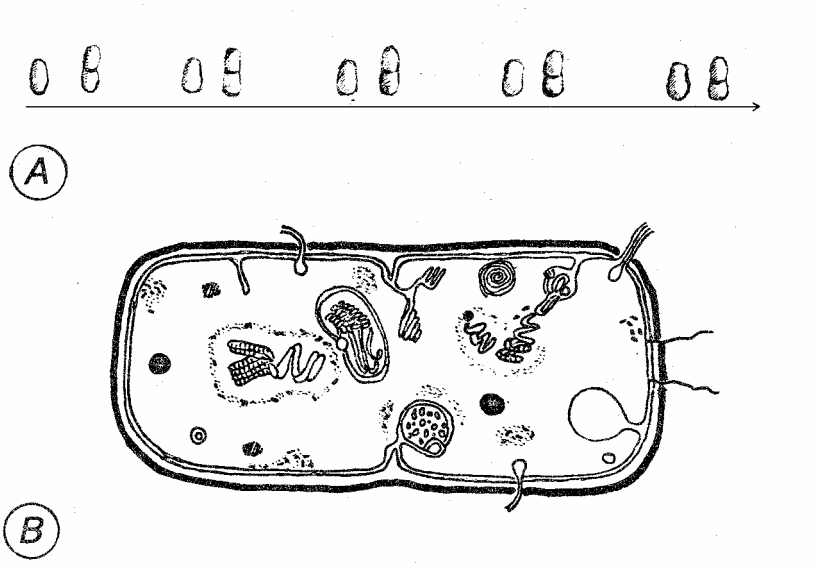

Fig. 3-2 A. Life cycle of a rod-shaped bacterium (Bonner 1965, plate 1.) B. Diagram of typical anatomical structures common to many bacteria (Hanker a.Linton 1971, Fig. 9.1)

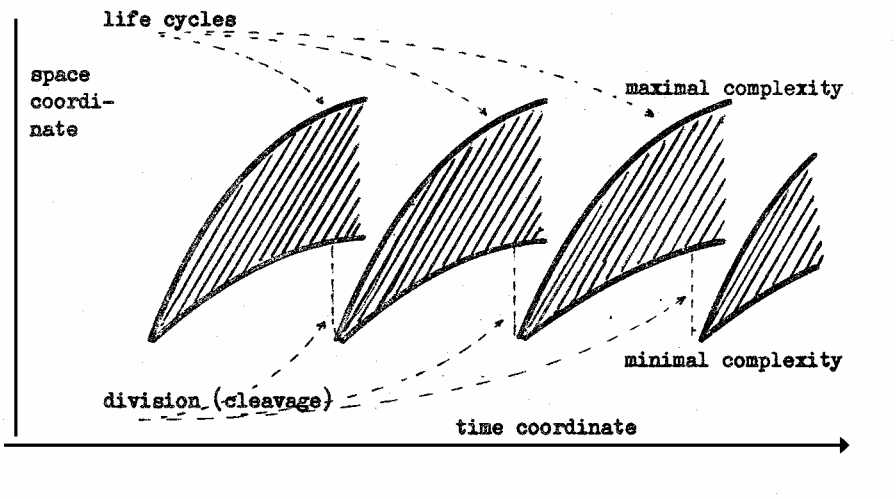

Fig. 3.3 Continuity of the life cycles.

The specific, extraordinary property of some points would serve as a non-arbitrary criterion of that mental division between the single periods. Now, are such points recognizable within the continuous line of periods? Because structural heterogeneity increases along the time vector and still does not exceed a species specific maximum, there is such a point at which the heterogeneity drops back again, in a relatively short time, to the species specific minimum.[47] This apparent reversal of the general trend (towards greater heterogeneity) marks the transition between the parent and its offspring.[48]

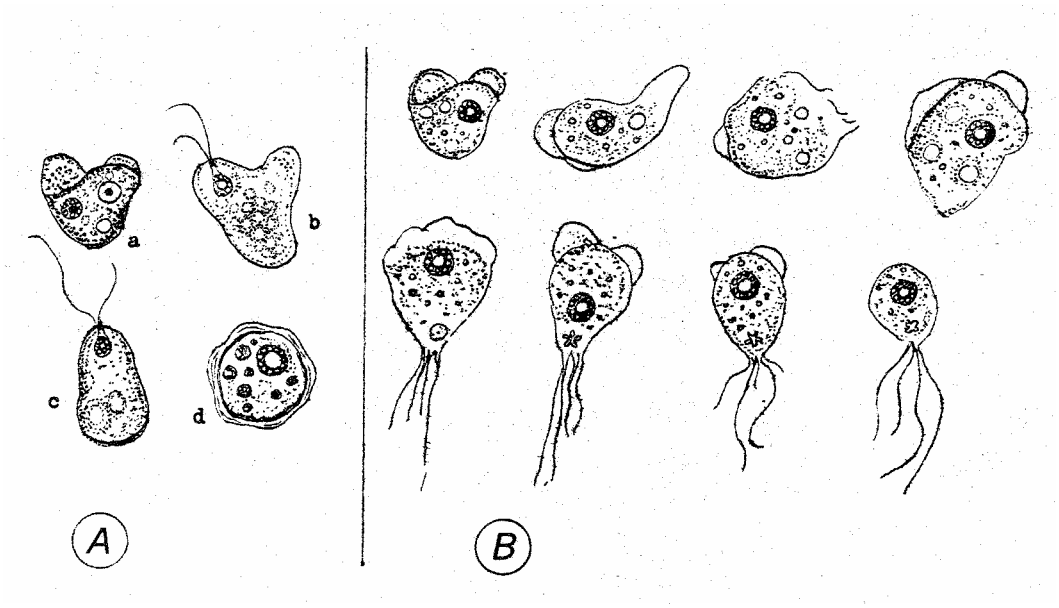

Fig. 3.4 A. - The different phenotypic forma of Haegleria gruberidt.bistadialis)2 a - ameboid state, b - transitional state, c - flagellate state, d - cyst state. (Kflhn 1971,Fig.lo8) B. - The gradual transformation of the ameboid state into the flagellate state. (Willmer 1960, Harrington 1970,Fig.3-6.) (See section 3.9)

The life cycle, as delimited by the above mental process, constitutes the minimal notion of living organism, and, we should add, genetic study cannot start until there are at least two such

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[47] Nozeran calls seed in. plants "the zero point for a plant" (1971/56).' Bonner uses size as an index to find the limits of a life cycle and writes: "We could say that the life cycle is framed by the point of minimum size and the point of maximum size" (1965/14). The situation, however, is more complex. When adapta-tional transformations take place, the criterion of size may become ambiguous. "What we single out as a whole, or where we draw the 'partition boundary' will be determined by whether we can—isolate recurrent pattern of coherent structures of a distinct kind which we do in fact encounter" (Hayek 1964/336).

[48] Remarks such as, for instance, that of Coleman: "The decisive fact is...that in higher forms of life "generation" is no simple event. Adult organisms...do not produce directly a new adult form but only a fertilized egg" (1966/35), should not create a wrong impression that in the case of unicellular organisms the generation is a "simple" event. In fact, "the cell cycle shows in miniature two of the most important characteristics of differentiation systems: morphogenesis, and the periodic synthesis [of its structures]" "We are only at the beginning of the process of unravelling a temporal complexity in the cell cycle which matches the spatial complexity of the cell" (Mitchison 1973/189, 209. See also Thrasher, 1971, Berill, 1971/57-76, Bonner 1973/3-4).

minimal units.[49]

The term "cycle" might wrongly suggest that a given entity was brought back to its initial state. In reality, "life cycle" means a real, unidirectional, physical change. Repetitivity of this change is observable not within this change but comparing entitatively different "life cycles." The nature of continuity between the individual "life cycles" is not quite obvious. Certainly it does not mean the entitative identity of material elements which were built into the evolving structures of consecutive "cycles." It means that the overall pattern of transformations was identical or at least similar.

The idea of the "life cycle" converges with the "Weismannian" notion of phenotypic phenomena.

> The "life cycle" as a whole constitutes here the primary observational evidence and the reference point both for further study of its details and for their proper interpretation. " — the life cycle is the central unit in biology. The notion of the organism is used in this sense, rather than that of an individual at a moment in time, such as the adult at maturity. Evolution then becomes the alternation of life cycles through time; genetics the inheritance mechanisms between cycles, and development all the changes iri structure that take place during one life cycle... The life cycle is a summation of all the molecular or biochemical steps, one following another in a well-ordered sequence..."
>
> (Bonner, J.T., 1965/3-4).

The most important property of the "life cycle" concept is its

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[49] "In the absence of temporal homogeneity we can nonetheless discern in the history of the enduring thing a permanence of characterization in its mode of change...although the serial type requires, for its recognition, reference to other things characterized by it, since unlike the rhythmical it is not repeated in, or does not characterize, the same individual thing, but only a class of things.. ."(Woodger, 1967/190-1).

dynamic character. The "life cycle" is a process, and any true part of it is a process, too. Any part of it reveals not a three- but a four-dimensional structure. Consequently, no static entity can be identified as a true part of the "life cycle."

There is another point to be raised here. The "life cycle" as a whole means a continuous transformation from a more homogeneous state towards a more heterogeneous one. So, generally speaking, the parts of the "life cycle" reveal the same characteristic, too. In other words, both "life cycle" and its parts, or details, are dynamic, epigenetic events.[50]

The essentially holistic notion of the "life cycle" is opposed by the analytic Mendelian notion of the hereditary trait. In the case of the hereditary trait, a special new methodological approach is applied. Individual life cycles are compared one with another, point by point. As a result of this procedure, some observational phenomena, or hereditary traits, are picked out from the whole context of the "life cycle."

We will now have to reflect upon this process of the selection of traits.

3.4 Fragmentary units of heredity — hereditary traits

Unlike the "Weismaimian," the "Mendelian" notion of phenotype is static in the overwhelming majority of cases. It is a fragmentary structural pattern which has appeared upon a more or less arbitrarily selected stage of the "life cycle." The selection of a "Mendelian" trait is thus double-fold. First, it selects among different stages of the intrinsically indivisible and continuous "life cycle" process. Secondly, it selects a part of the whole static pattern observed upon this mentally "frozen" stage.[51] The colour

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[50] "We can hardly doubt that in the living world there is a general phenomenon which can be termed anamorphosis, that is, increase in order and organization which is found in the development of an individual as well as in evolution" (Bertalanffy 1972/27). We may recognize the same idea in the following statement: "life is a process... the unit of life is not a particle or static body ...but has to be a unitary elementary process …" (P. Weiss 1958/140). See also other similar enunciations registered during Gerard's Symposium on the nature of life (1958), especially Brink ("dynamic system"), Schmitt ("process"), Reynolds, Wright (metabolic turn-over and development), Hotchkiss (repetitive production of ordered heterogeneity within an unordered environment).

[51] The obstinate refusal to recognize the dynamic (epigenetic, developmental, physiological) nature of "life cycle" and the reduction of the notion of an organism to its "frozen" structural, transient form observed upon an arbitrarily selected level of the temporal dimension was analyzed by Woodger (1967/ 302ff., 422ff.). See also Whitehead's suggestion about the role of mathematical mentality in the development of this a-temporal static way of representing four-dimensional observational phenomena (1919, in: Kockelmans, 1968/414ff.)

of eyes, for instance, is a fragmentary static property of a greater structure which has appeared relatively late during the "life cycle." "Some biologists prefer to examine the morphological features of the organism, the shapes of leaves, of bones, of flowers, of genitalia. Others choose to study less obvious properties like tolerance to various salt concentrations, light intensities or velocities of response to intelligence tests. Still others are concerned with resistance to disease...with pigmentation or the nature of the blood antigens and antibodies. All of these things are different aspects of the phenotype. Some of these can change overnight, others show greater constancy" (Lewis § John 1972/13).

We might say that "Mendelian" genetics starts its investigation of hereditary phenomena where "Weismannian" had come to an end. "Mendelian" genetics simply presupposes the concept of the "life cycle," but it goes beyond it in making a comparative study of selected traits.as they appear within the context of their respective "life cycles." The selection of traits for study constitutes the starting point of "Mendelian" genetics, and we will have to consider now the criteria of this selection.

The "Mendelian" notion of hereditary phenomena starts with a detail of the "life cycle," a detail which was recognized by comparing the differences existing between "life cycles." This detail is sorted out from the non-hereditary details of these "cycles," the sorting out being based upon the two independent criteria mentioned in the definition of the hereditary trait. Now, the relative independence of these two criteria creates a logical, purely formal problem as to the logical adequacy of the division between the hereditary and the non-hereditary, or the genetic and the acquired, traits of the "life cycle." From the point of view of pure logic, two independent criteria divide a set of entities not into two but into four different sub-sets. In our case, a suspicion might arise that the application of these two criteria leaves two sub-sets of phenotypic traits unmentioned.

In order to verify this suspicion, we will construct a model of the classification of phenotypic traits based upon the two criteria implied by the definition of the hereditary trait. Then we will check which of the model sub-sets is non-empty. Finally we will analyze the problem of the

nature and the origin of the members of different sub-sets.

3.5 The model of classification of phenotypia traits

Following the original idea of phenotype, as defined by Johannsen, we are not restricting its definition. Phenotype means any observable trait of the life cycle.

Our model of the classification of phenotypic traits does not introduce anything new into the definition of the hereditary trait. It simply makes use of the explicitly stated criteria, which according to the accepted views are basic for the recognition of the hereditary traits within the whole set of phenotypic traits.

This classification might be represented as follows:

	GROUPS OF PHENOTYPIC TRAITS			
CRITERIA	1st	2nd	3rd	4th
1) repetitive appearance within the successive life cycles	+	+	-	-
2) dependence upon environmental influences	-	+	-	+

Table 3.1

Anticipating the results of the analysis which will be carried on later, we will tag the above four groups with a proper name. That will simplify our terminology. The first group will be referred to as the "basic" phenotype, the second group as the "adaptive" phenotype, the third as "individualizing" phenotype, and the fourth as the "traumatic" phenotype.

Before we pass on to the discussion of the possible application of the proposed classification of descriptive traits abstracted from the integrated pattern of the life cycle, we should explain more fully the notion of the environmental influence.

3.6 The notion of the "environmental influence"

The environmental influence means a physical or chemical influence of any material entity present in the surroundings of the given life cycle. The notion of the influence should be distinguished from the notion of "triggering effect." In the latter case, a given physical or chemical influence releases a whole series of events within the body of an organism, and these events are not reducible to the environmental influence alone. Let us take an example. An external, environmental agent may exert a pressure upon the surface of my

skin and modify the external shape of my body. This modification has to be considered as caused by the environmental agent. But at the same time, the sensory nerve endings are sending a series of electrical impulses up to my central nervous system, producing, let us say, dilatation of the pupils in my eyes. Are the electrical impulses and the dilatation of pupils attributable to the environmental influence? We may say that the impulses were "released" by the environmental change, but that the difference between the "causal influence" and the "triggering" (release) influence" seems, intuitively, to be irreducible.

Let us take another example. The temperature of the body of a frog changes under the influence of the environmental sphere, and these changes are reducible to environmental influences. On the other hand, seasonal variations of temperature may trigger a complex series of events which in some animals leads to the appearance of thicker fur. It might be that the environmental temperature change really influenced the appearance of this phenomenon, but nonetheless it cannot be reduced, as a whole, to the environmental influence alone.[52]

Another important point must be stressed here. The environmental influence may be conceived of as "any physically possible physical influence," or as a concrete environmental influence registered here and now. Of course, we do not know any organism which could withstand "any possible physical influence." It means that the range of independence from the environmental influences as postulated for the 1st and 3rd group in our classification (see Table 3.1) has to be understood in the context of certain limits within which an organism reveals a virtual lack of dependence on the environmental sphere.

After these complementary explanations we may now pass to the discussion of the four separate groups of phenotypic traits. We will try to verify whether all of our four sub-sets representing different observational properties of the "life cycle" are non-empty.

3.7 The "individualizing" phenotypic traits

Looking at our classification scheme, one may ask whether the 3rd group of phenotypic phenomena is not absolutely imaginary. Would it be possible

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[52] We know, on the other hand, that physically different situations may "trigger" the essentially identical developmental process within the body. An unfertilized egg may start to develop in response to pricking, exposure to acids, hyper- and hypotonic solutions, or temperature shock (Hamburgh 1971/1). "The growth (regeneration) of adult organs can be stimulated not only by their partial resection, but equally well by functional overload" (Goss, 1969/269).

to demonstrate the existence of any structural or dynamic phenomenon which would be independent of the environmental influences and at the same time unrepetitive? In fact, it is possible. The antigens are such entities, for on the biochemical or, more generally, the subcellular level of bodily organization they fulfill the criteria set for our 3rd group of phenotypic traits. An antigen, in fact, is a rather highly complex chemical substance which displays physical properties quite unique among sexually reproducing organisms for the given, concrete life cycle. Antigens do not seem to play any role in the functional species specific events of the life cycle. Their origin, on the other hand, is irreducible to random environmental influences. They appear de novo in every single life .cycle and constitute an individualizing, distinctive trait of this particular life cycle.[53]

The variety of antigens is thus practically infinite, at least in relation to the number of actually living organisms. But there are other, descriptive traits of single life cycles which are unrepetitive, too, like the fingerprint pattern, some peculiarities of the overall pattern of skin pigmentation, of hair distribution and so on.

These and similar characteristics or "peculiarities" of individual life cycle are usually taken separately, as if their "ensemble" had no special, indivisible meaning at all. But is there any justification for this procedure? Is this "ensemble" of "individual peculiarities" really deprived of any intrinsic unity? In order to explain ourselves better, let us turn to the structure of the antigen which constitutes a biochemical "individualizing" trait of a given, concrete life cycle. If we were to try to break down a protein antigen into its parts, its uniqueness would vanish. It will be split into twenty basic aminoacids, and these structures, although characteristic of living organisms, are common to all of them. Only the whole antigen is Q unique.[54] Its parts are not. Similarly, only the whole pattern of hair colour

[53] The fact of the great diversity of antigens, the relative independence of developmental processes of the life cycle from the specificity (diversity) of antigens, the apparent lack of interference between the origin and properties of antigens and the other hereditary traits was realized by Sturtevant and Haldane as early as 1932 (Sturtevant, 1965/97).

[54] Antigens are so unique in their structure that the study of their nature is extremely difficult. The structure of antibodies (protein molecules which have a unique aminoacid sequence, so that it can interact selectively with the given antigen which has provoked its production) is only partially known. Only in some pathological cases are the incomplete antibodies (Bence-Jones proteins) produced, and the single molecules are identical enough to make their structural analysis possible. However, "it is worth noting that each patient excretes a unique [form of] Bence-Jones protein" (Mahler £ Cordes, 1971/132).

and distribution, of eye colour and shape, of skin pigmentation, of the peculiarities of the nose and ear shape, the whole pattern of fingerprints are unique. Fragments of this overall pattern are not. An individual life cycle is physically recognizable, identifiable because of this unique set of characteristics which are unique only as a whole. Baby animals are recognizable by their parents because of this unique pattern of macroscopically observable q traits. The case of monozygotic twins is a good exception from this rule.[55] Monozygotic twins are not unique either in.the macroscopic pattern of characteristic traits or in the biochemical structure of their antigens.[56]

The 3rd group of characters might be compared with the catalogue number of a single copy of a book. The copies of the same edition of the same book may have a different catalogue number, and it will help us to identify single concrete copies of them.[57]

3.8 The "traumatic" phenotypic traits

In the case of living organisms, there is another set of observable characteristics which are also unique, but essentially reducible, in the sense of their origin, to the environmental influences. As every actual crystal shows some deformations of structure, peculiarities of colour and so on, which are all directly dependent on the history of its environment, so may the same be observed in the case of the living organisms, or, rather, life cycles. Some environmental influences produces wounds, burns and other damages. The

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[55] The theoretical meaning of the "twin case" was obvious to Weismann (1887, in: Moore 1972/68-71). See also Galton 1875a and 1875b; and Poulton's comment to the above-mentioned text of Weismann, in: Moore 1972/69).. It seems that the meiotic process affects hereditary individualizing phenotype, while mitotic division leaves it unchanged.

[56] Elsasser (1969/83) stresses this uniqueness of structural form as one of the essential characteristics of all organisms. He does not, however, seem to realize the difference between the genetically determined individualizing traits (3rd group of phenotypic phenomena) which certainly are not common to all living forms (cfr. for instance the case of vegetative reproduction), and the environmentally conditioned individualizing traits (4th group) which appear in non-living structures, such as crystals, for instance (See Weisskopf,1969/33).

[57] The astronomer Gamow (1954) postulated that "the hereditary properties of any given organism could be characterized by a long number written in a four-digital system..." (p. 318). The double meaning of the term "characteristic" is quite obvious here. Hereditary "basic" traits are "characteristic" but "common" to any single specimen of a given species. Antigens are "characteristic" to the single specimen's "common," i.e., "species specific," characters.

pattern of these damages is unique because of the randomness of environmental influences. If these damages were not regenerated, repaired, or the repair was not completed, the remains of the original environmental influences would constitute a permanent unique individualizing pattern, characteristic for a given concrete life cycle. The elements of this pattern belong to the 4th group of phenotvpic characters. They are not hereditary, because they are not repetitive, either trans-individually, as the elements belonging to the 1st and 2nd group, nor immanently, as antigens, for instance. Antigens, in fact, although trans-individually unique, are highly repetitive within the sphere of the single life cycle. Their repetitivity as well as their origin has to be explained in terms of repetitive de novo formation, and so, in spite of their trans-individual uniqueness, they belong to the sphere of hereditary phenomena.

The 4th group of observational traits is "individualizing" in the same sense in which different copies of the same edition of the same book are differently affected by time and usage, so that although just after printing and binding process they were practically indistinguishable, now they are easily identifiable.

3.9 The "adaptive" phenotypic traits

There is a large amount of evidence for the existence of phenomena which are obviously parallel to some environmental changes but which still cannot be adequately explained without reference to the intrinsic properties of the organism itself. Traditionally these phenomena were treated as an example of adaptation, but in modern genetics they are referred to as a case of "phenotypic flexibility" (Thoday 1953). Let us look at some examples:

1) "In lower vertebrates, sex reversal can sometimes be brought about by changes in temperature" (Mittwoch 1970/116. See also Yost 1970/119; Beatty 1970/14; Chan 1970/60, 67-8; Blackler 1970/80; Viaimey-Liaud 1971/11-17; Gallien 1973/9).

2) There are strains of *Escherichia coli,* the common bacterial form permanently present in human intestines, which can grow and reproduce on two or three hundred different types of nourishment. If the *E. coli*

are fed, for example, on lactose, they will make a particular set of enzymes; if the lactose is replaced by glucose, a new set of enzymes will appear "de novo" (Glaser 1968).[58]

3) *Espejoja mucicola,* a protozoan organism which in the presence of mucin has a large and complicated "mouth," when placed in distilled water loses all these structures and becomes a very active migratory form with only a trace of the original mouth region (Faure-Fremiet and Mugard 1949).

4) *Naegleria gruberi,* first described by Schardinger (1899) and by many others ever since, undergoes a rapid (30-80 min.) transformation from ameboid to flagellate form and vice versa, obviously in answer to the change in its environment. The same organism may also encyst within a tough capsule and become dormant for long periods. In higher tem peratures N. gruberi can form epithelium-like colonies (Willmer 1970/155-63; Kuhn 1971/79; Fulton 1972). (See Fig. 3.4).

5) "*Celloniella palensis*, a colonial Chrysomonad occurring in cold, swift brooks, varies tremendously in form according to local conditions. In strong currents, the alga forms wavy, leaf-like colonies up to 2 cm long. The jelly sheath is held fast to stones by a stalk and spreads in to irregularly branched lobes. At the edge of the lobes and in the region of the stalk are numerous cells, each with a yellow-brown, cup- .shaped chromatophore—Where water plunges over a rocky edge, Celloniella forms a gel structure entirely different from that in running water. It is a crust consisting of several layers whose margins contain calcium carbonate granules...Finally, beneath an overhang where the water trickles down and drops away, the Chrysomonad forms sacs. These are filled with a liquid, and the cells lie in the sturdy surface layer, which contains numerous CaC03 granules... If the stones with pieces of crust are placed in running water, arches arise in the course of one or two days in which cell division is rapid; and in the course of the next four days irregularly cylindrical extensions several millimeters long, pointed at the end and with lateral bulges, begin a transition to the leaflike colonies. If pieces of leaflike, encrusted, or

[58] There is a long-lasting discussion on the right interpretation of the mechanisms involved in this kind of phenomenon (see Mason 1953/437-8). More recent evidence concerning the non-random control of gene-action in procaryotes (see Herskowitz, 1973/411-423) seems to diminish credibility of a mutational interpetation of the facts.

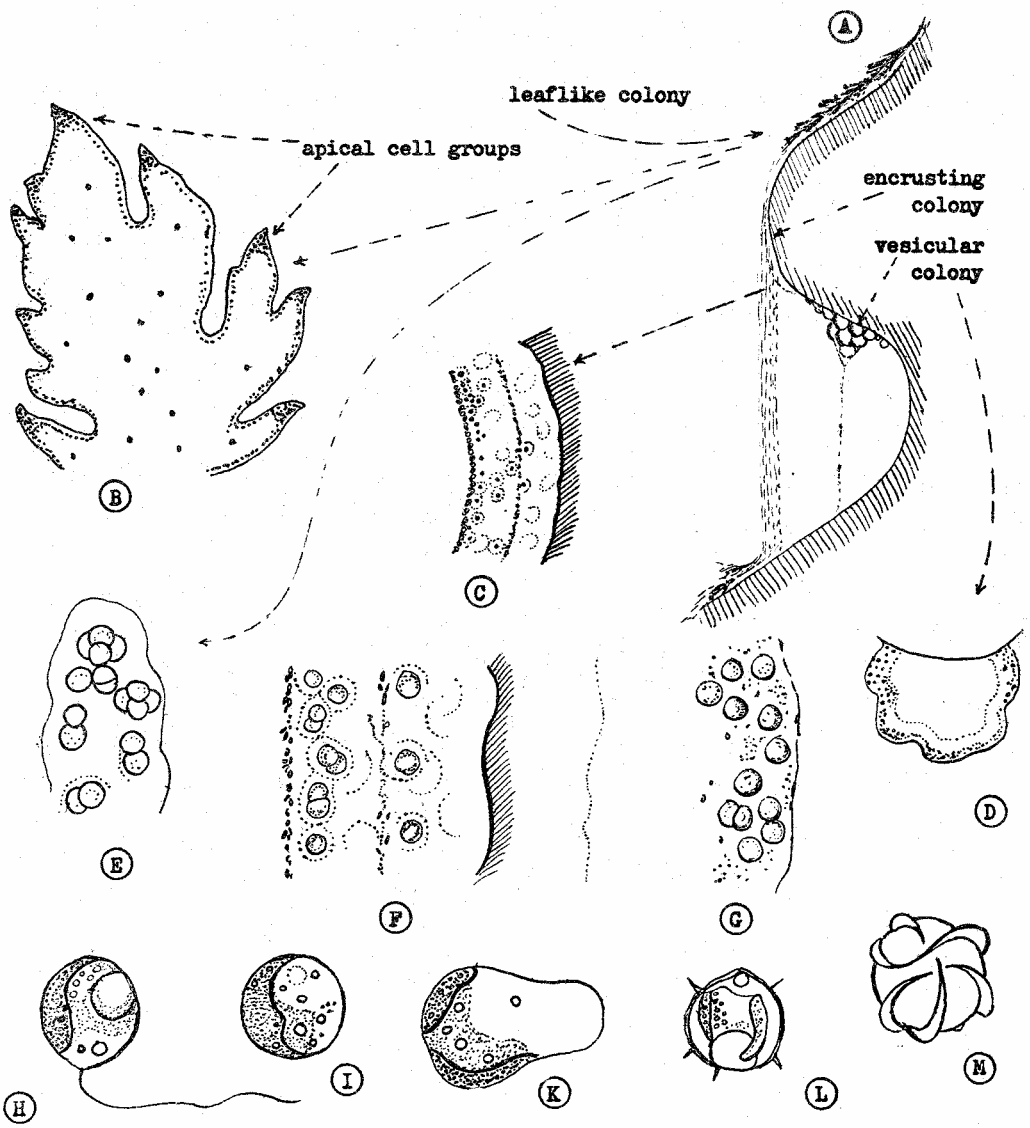

Fig. 3.5

Phenotypic adaptation in alga *Celloniella palensis.*

A,B - leaflike form; E - end of a lobe, highly magnified; C,F - encrusting colonies; D,G - sac colonies; H - swarmer cells; I - resting cells; K --cell in ameboid movement; L – cyst (optical section); M – cyst (surface view).(After Pascher, 1929 and Kühn,1971 fig.173) (See section 3.9)

saclike colonies are placed in still water, the formation of motile forms is triggered. After only a few minutes the cells swim out, each with one long flagellum. These swarmers can divide and can transform into amoeboid forms, which creep around with blunt pseudopodia. In cool water they attach and begin to make jelly" (Kühn 1971/130-1). (See Fig. 3.5).

In all the above examples the observed changes were parallel to the changes in the environmental sphere, and completely reversible within the same, single life cycle. The capacity to undergo these transformations is thus species specific and dependent upon the environmental influences. We may conclude that at least in some forms of life the phenomena fulfilling the criteria of the 2nd group of phenotypic traits may be observed. They show a double parallelism. They follow the pattern of environmental "fluctuations" and at the same time they reappear with a non-random repetitivity in the context of continuous series of life cycles.

3.10 The "basic" phenotypic traits

In this case the phenomenon of repetitivity is most obvious and the relative independence from the environmental "fluctuations" most pronounced. The phenomena of the 1st group constitute the basic, necessary element of life in general, and of heredity in particular.

Examples may be drawn from any level of bodily organization. Both structure and dynamics of digestive, respiratory, metabolic, excretory or reproductive machinery are repetitive down to their detailed biochemical organization. From the biochemical point of view, greater repetitivity of structural and dynamic pattern than that we observe in basic, common metabolic processes is physically impossible (See Green and Goldberger 1967).

3.11 Some general remarks concerning the proposed classification

Now, how may we summarize the results of our classification? It has revealed, first, that two different forms of individualizing traits can be recognized within the whole set of phenotypic characters. One (the 4th group) is lacking any epigenetic origin and is reducible to the purely environmental influences of the inanimate matter which constitutes the surroundings of an organism. The second form of the individualizing traits (3rd group) appears, on the contrary, as a result of typically epigenetic process, and although it is unique with respect to other organisms, it shows a patent repetitivity within the immanent sphere of the single, same "life cycle."

Secondly, our classification has revealed two different forms of influence which the inanimate environment exerts upon the sphere of the organism. One form of this influence is purely physico-chemical, and it is evident in the case of the 4th group phenomena. The other form of this influence we have called "triggering effect," and this provisional term will be analyzed and defined in a more precise way in the next chapter of our essay. This "triggering effect" is

manifested in the 2nd group of phenotypic traits.

Finally, our classification has revealed clear-cut differences between the first three subsets (groups) of phenotypic traits, on the one hand, and the fourth one, on the other. These differences are represented in Table 3.2.

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Group	Examples of phenotypic traits characteristic for the group	Repetitivity (structural)	Origin	Repair and regeneration	Specificity
1st	Metabolic, reproductive, excretory and other physiological systems	External and internal[59]	Epigenetic	Observed at least during development	Species specific
2nd	Adaptive, reversible transformations of the 1st group phenomena	External, and internal	Epigenetic	Observed at least during development	Species specific
3rd	Antigens (molecular , organellar, cellular) ; fingerprint patterns, pigmentation, patterns and the like...[60]	External (veget. I reprod.) and internal	Epigenetic	Observed	Race specific[13]
4th	Mutilations of any sort, weight, impetus, shape, temperature in poikilotherms . . . etc..	Random	Environmental causality	Absent	No specificity

TABLE 3.2 .

[59] External repetitivity means here the identity of the heterogeneous pattern as revealed by comparing the two different "life cycles." Internal repetitivity means that a heterogeneous pattern is repetitively observable within the same "life cycle." Muscle cells, myofibrille, myosin molecules, are repetitive both externally (they are.identical both in the same organism and in different specimens of the same species) and internally. Antigens, on the other hand, are repetitive only within the sphere of the same organism. But in spite of their essential uniqueness, they are more similar within the same race population.

[60] See, e.g., Penrose, 1963/933ff., or Glass, 1953, in Srb et al., 1969/295ff.

Summing up, we may say that:

a) The definition of the hereditary traits divides the whole set of phenotypic characters of a living organism into four non-empty sets of characters.

b) One of these sub-sets, the fourth, is composed of traits which are causally reducible to the environmental influences, and this reduction is *complete.* In other words, the fourth group of phenotypic characters originates as a result of purely physico-chemical environmental influences.

c) Three others groups are not reducible one to another but, because they are believed to be irreducible, in the sense of their origins, to environmental influences, they represent hereditary traits of the "life cycle."

In the first and second group of traits, the epigenetic nature of their origin is obvious enough (see Saunders, 1970/109 ; Keynan, 1973/86 ; Mitchison in: Balls and Billett, 1973/1). The phenotypic traits classified in the first group constitute the essence of the "life cycle." In the "favourable" environmental conditions, the phenomena of the second group may not appear at all (see Puck, 1957/14; Williams, 1963/256; Ephrussi, 1970/18; Willmer, 1970/2; Kluge, 1971/3-9; Reznikoff, 1971/133; Nozeran, 1972/51, 54), while the phenomena of the third group are also deficient in the case of vegetative reproduction.[61] So the phenotypic traits of the first group constitute the minimal set of observational evidence which is irreducible to environmental influences. The bacterial cells, which multiply in a non-sexual way and are thus deprived of the hereditary "individualizing" traits (3rd group) still reveal all the essential phenomena of the first and second group of phenotypic traits.

" … The newly formed cell differs from a cell about to divide not only in size but...in its composition, and this composition changes

[61] The cells cultured *in vitro* lose their function, their organ-specific antigens, their capacity for self-recognition and reaggregation (see Eagle, 1965).

> qualitatively in a fixed sequence throughout the cell cycle...The bacterial cell behaves as a unit in that all its components are duplicated together in each cycle and that it changes its relative composition in appropriate ways in response to changes in its environment" (Donachie et al, 1973/30).[62]

We will now discuss in some detail the epigenetic origins of the phenomena which were classified in the third group of phenotypic characters.

These traits for years constituted the main object of genetic study. As we have seen, the hereditary characters of this group are not directly involved in the functional and developmental events of the "life cycle." For this reason, it was easy to study their "re-appearance" pattern in a practical separation from the more essential mechanisms of the "life cycle."[63] For the sake of simplicity, their origins within the "life cycle" were also left aside. In this way the main feature of the first groups, namely, epigenetic, de novo formation, was seldom mentioned in the context of the phenomena belonging to the third group of phenotypic characters (see Beadle § Tatum, 1941/499).

For this reason, we will reflect for a while upon the details of the transformations which lead to the appearance of a hereditary trait belonging to the third group of phenotypic characters.

3.12 The hereditary individualizing phenotypia trait (3rd group) and its developmental path

Let us reflect for a while upon the nature and origin of an "elementary" "hereditary character" such as colour of the eyes. It is recognizable only after the head tissues and the eyeballs are formed. In other words,

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[62] A sexual type of reproduction seems to be essential for the appearance of the genetic individualizing traits (3rd group). "If man reproduced his kind the way bacteria do [i.e., in a non-sexual, vegetative way -PL] a grown man at 25 would more or less abruptly become two young men in his own exact image..^ rather large family could eventually be built up by this process, but all its members would be monotonously alike in appearance, abilities, temperament and vigor...The same would be true of every family.r.There would be families of burly, competitive athlets, and others made up exclusively of gray-eyed introverts liking nothing better than to write sad poems on the haunting loveliness of subdivision" (Hotchkiss and Esther Weiss, 1956, in: Srb et al., 1970/31).

[63] As Beadle and Tatum wrote: "...A number of limitations is inherent in this approach. Perhaps the most serious of these is that the investigator must in general confine himself to a study of non-lethal heritable characters. Such characters are likely to involve more or less non-essential so-called "terminal" reactions. The selection of these for genetic study was perhaps responsible for the now disappearing belief that genes are concerned only with control of "superficial" characters...(1941/499).

a single fertilized egg cell has to multiply, the anatomical structures of the embryo have to be relatively differentiated,, before the colour of the eyes will appear. The colour of eyes results from the fact that the great number of the specifically (in the biochemical sense) equipped cells are distributed in a limited area of the internal surface of the iris. Those cells are able to produce a special yellow, brownish or dark brown sort of pigment which is called melanin. Depending on the qualitative and quantitative properties of this pigment within the iris cells, the iris, which is originally quite transparent, becomes grey-blue, blue, violet, green, brown or almost black. The melanin-producing cells are selectively distributed in different parts of the body, and they develop from the early embryonic, undifferentiated ectoderm, together with the neural tissues. During embryogenesis they undergo a specific form of differentiation (epigenesis) which leads to the appearance in them of the special enzymatic complexes capable of producing the melanin pigment. While this differentiation takes place, the cells themselves migrate from their source in the neural crest to the eyeball primordia which at the same time undergo another form of differentiation leading to the formation of the light- and colour-sensitive receptors of the retina and of other structures determining the proper functioning of the organ.

The black-eyeness (or violet-eyeness, and so on) is not produced by the presence of the melanin-producing machinery in a single melanophore. It is the result of the symmetrical distribution of many melanophores in both eyes. Consequently, albinism, the lack of pigment in the eye's iris, in the hair and in the skin, is not provoked by the lack of the melanin granules in a single melanophore cell. We know that in the case of albinism, special enzymes necessary for the production of the pigment. (o-Diphenol oxidase) are missing. So if one says that "albinism results from the lack of the o-Diphenol oxidase" (Mahler § Cordes, 1971/805), it does not mean that the lack of a single enzyme molecule could explain the appearance of the albinism. Hundreds and thousands of cells, hundreds and thousands of enzyme molecules have to be present in order to produce the "colour of the eyes," and a proportionate number of cells or molecules of the enzyme have to be missing in order to produce the observable trait of albinism.

Melanophores do not appear *in instanti.* They constitute the final stage of a partial "life cycle" of a given body.

If we forget about the bodily and developmental context in which

the colour of eyes appears, we would not find any reason (any physical reason) why the melanophores are not present within the lens of an eye, or in the joint cartilage, or at the tip of the tongue.

The gradual and physically indispensable steps which lead to the production of the specific thyrosinase molecule, all the complex biochemical machinery which enables the melanoblast to migrate, the complex system of the migratory movements control, all this should be put together in order to make a physico-chemically sound explanation of a hereditary trait such as the colour of the eyes distributed in a non-random way in some body areas.

Microscopic	unicellular egg ↓	(cell divisions)
scale	Multicellular blastula ↓	(cell divisions, migration of cells)
of observation	Multicellular gastrula ↓	(cell divisions, migration of cells)
	Neural folds within the neurula ↓	(cell divisions, migration of cells)
Macroscopic	Primary optic vesicle within the neural plate ↓	(cell divisions, migration of cells)
scale	Outer layer of epithelium within the optic cup ↓	(cell divisions, migration of cells)
of observation	Grey-, blue-, green-, brown-, or black-eyeness	
	→ → → → time dimension → → →	

The simplified scheme of events which lead to the formation of grey-, blue-, green-, brown-, black-eyeness in mammals (see Fig. 3.6; see also Spemann, 1967/41ff.; Kühn, 1971/262ff.; Waddington, 1962/5).

Of course, from the level of neural folds on, the processes sketched above are going on symmetrically, so that the colour of one eye is not much different from the colour of the other.

The above description of the process of the formation of grey-eye-ness (and all the other hereditary colours of the eyes) is very much simplified. The right number of cell divisions, the right direction of cell migration,[64] the internal differentiation processes in each single melanoblast, are

[64] On the problem of cell migration, see P. Weiss,(1968/24-95) and Trinkaus(1968)

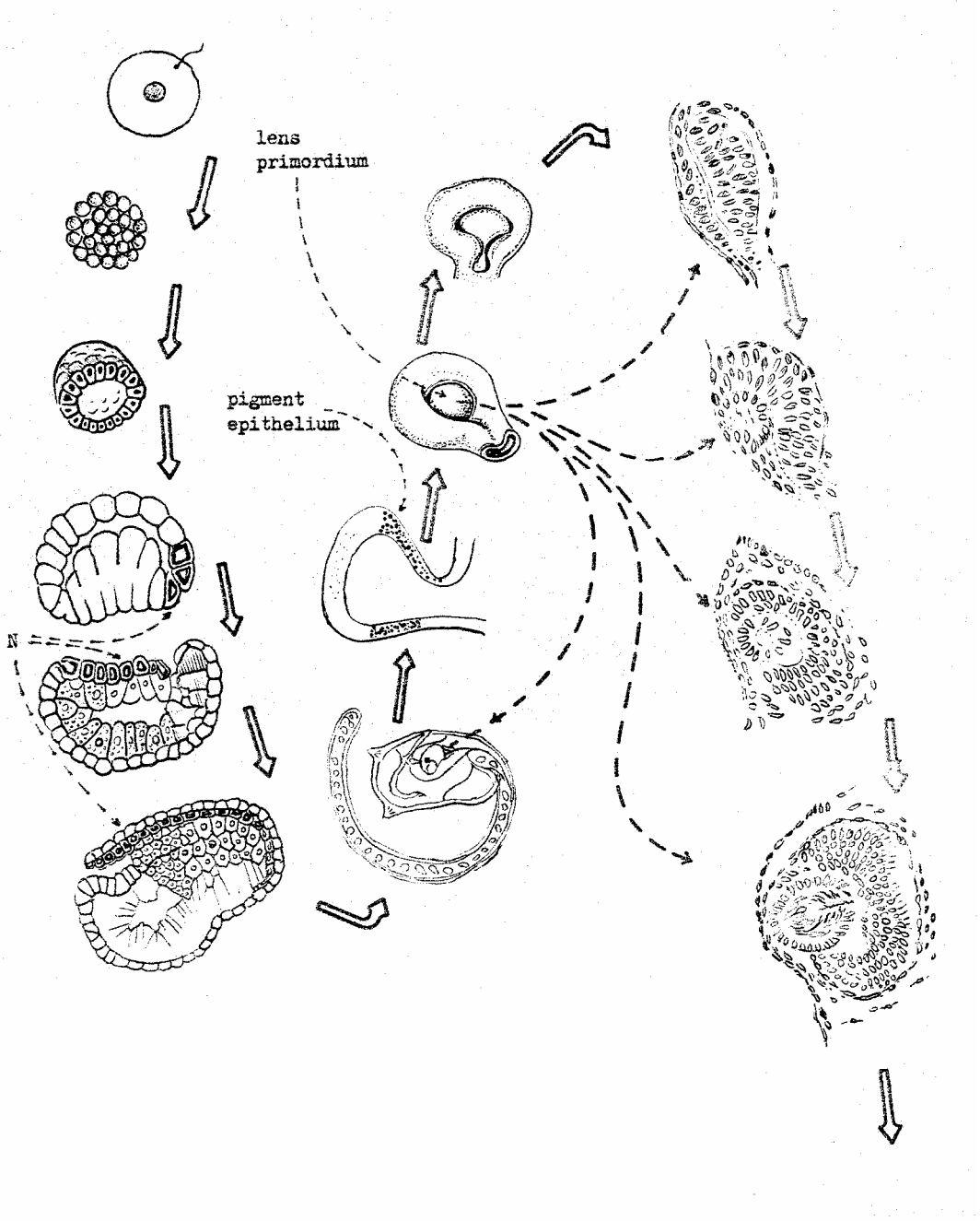

Fig. 3.6 Some selected stages of-the eye development in amphibia. N - neural folds. Note the change of the magnification scale between different elements of the graph.(After Kühn 1971, Figs. 339, 541, 368)

not only extremely complex but are still only partially known. Yet all the developmental steps enumerated above constitute a physically necessary condition of the re-appearance of an apparently "simple" trait such as the colour of the eyes. Analogous analysis might be made with any other of the genetic (hereditary) traits such as colour and shape of hair or bristles, the shape of wings, the pattern of papillary lines, the antigenic properties of blood cells, the skull bone racial traits, and so on.[65] The only observable physical phenomenon recognizable in the living organism (upon any arbitrarily selected scale of observation) which has no repetitive developmental history is the "traumatic" (4th group) phenotype we were talking about in the preceding section. In the case of this element of the phenotypic description, a concrete, environmental influence (thermal, mechanical, chemical) provides a physically adequate explanation for the appearance, the origin of the trait. All the other innumerable traits, whether the appearance of alpha-, beta- and gamma-crystalline proteins in the vertebrate eye lens, for instance, or the appearance of insulin in beta cells of the islands of Langerhans in the pancreas, whether the appearance or disappearance of a new biosynthetic molecular mechanism in the bacterial cell which adapts itself to the environmental changes, or the adaptive transformation of mammalian organs such as liver or kidney (cfr. Goss, 1964), are always traceable back to the single egg cell.

The physical properties of a hereditary trait which is observationally selected in the adult form are determined by the previous developmental transformations which inevitably lead to the egg, so that no hereditary trait is separable from its "developmental path," however arbitrary is the process of its selection among the other traits.

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[65] Dubois and Croisille (1970/88-9) describe another impressive example of epigenetic transformations, this time concerning the development of the primordial germ cells in birds. They are transported passively by the "pregastrular and gastrular caudocephalic morphogenetic movements," then they "swarm out of the endophyll and invade (by ameboid movements) the anterior vascular network." They are transported passively by the blood stream, but in the vicinity of the gonadal primordia "they recover an autonomous activity which is directed by a selective and specific chemotactic mechanism. The transit through the vascular route appears as an adaptive process, consequent upon the remoteness of the gonocytes..." "...Finally it appears from the present study that the germ cells do not remain passive and unchanged during ontogenesis. They undergo profound ultrastructural, histo-chemical and physiological changes, and have to be considered as very highly specialized cells..." (See also H. Peters in Harris and Edwards, 1970/91-101).

Consequently, the distinction between a given hereditary trait and its "developmental path" is only a mental one. It is not possible to produce this end effect without the preliminary physical events we call the "developmental path," or a physically equivalent series of events.

3.13 The concept of the developmental path

Even if we have broken down observationally the whole adult living body into a number of hereditary traits, basic, individualizing or adaptive, we have to admit that they do not appear out of nothingness. They are the end-points of a temporal series of physical events, which, if we look back in time, converge with the "neighbouring" series in the single cell of a fertilized egg. The "developmental paths" of different hereditary traits are different and have to be different because physical laws cannot be violated, and the different traits are prepared by different physical events, not by the same ones. The existence of a hereditary trait postulates the existence of an appropriate "developmental path" and, at the same time, is *explained* by this "developmental path."

3.14 Biochemical level of developmental path phenomena

Two important facts have to be realized here. First, even if we could dissect the adult form of an organism down to its single chemical molecules, their appearance in the adult form is due to the developmental process which involved much more complex structures than the "end product." The production of a hemoglobin molecule, for instance, involves many preliminary synthetic stages from the synthesis of aminoacid molecules up to the synthesis of two pairs of different polypeptides (alpha and beta polypep-tide) and the non-protein complex protoporphirine molecule, the heme. Auto-trophic organisms can grow successfully in an environment composed of water, carbon dioxide and some mineral salt provided that light energy is available. Yet their molecular structure is essentially as complex as the structure of a metazoan egg, as far, at least, as their cytoplasm is concerned. This means that every single macromolecule which is physically necessary for their normal biochemical processes is built "de novo" from the molecules of water, carbon dioxide and mineral salts present in the environment. Consequently, each such functional macromolecule (an enzyme molecule, coenzyme molecule, cell-membrane mureins, phospholipids, polynucleotides, and so on) is not only a hereditary trait of those simple organisms but the end stages of a very complex synthetic process, quite analogous to the developmental path

of multi-cellular hereditary traits observable in pea plants or Drosophila flies. The "de novo" formation of structures is not limited to the macro-atructures of a whale or an elephant. The *"de novo"* formation process is observable in every structural element of a living body. Every living organism, including blue-green algae and pleuropneumonia-like organisms up to man's organism, are able to synthesize *"de novo"* an impressive variety of aminoacids, sugars, carbohydrates, purines and pyrimidines, and the like.

3.15 The "metabolic turnover" phenomenon

Radioisotope studies have revealed that every structural part of any living organism is not only built *"de novo"* once, but all the details of the structure are constantly renewed, "old" bricks being thrown out, or digested, and the new ones synthetized and replaced in the proper place and order.[66] "From the use of isotopes as tracers...results the idea of the *dynamic state* of body constituents...*stability* is maintained by flux..." (Waley, 1969/148).

> "It was thought [before] that once cell components, such as proteins or membrane lipids were synthesized, they remained intact for the lifetime of the cell.. .[after Schoenheijner et al (1930's) radioisotope studies].. .it was found...that the proteins of the liver cell exist in a dynamic steady state, in which a relatively high rate of synthesis is exactly counterbalanced by a relatively high rate of degradation" (Lehninger, 1970/282).

The same author adds a whole list of the "half-life" cycle of different chemical components in rat tissues in vivo (see also v. Bertalanffy, 1972/26, and P. Weiss, 1961a). The protein synthesizing apparatus undergoes rapid degradation and the *de novo* synthesis occurs with fantastic speed.

> "...each liver cell in the adult rat synthesizes 650 ribosomes, 650 5S RNA and 11,000 molecules of tRNA each minute..." (Thrasher, 1971/154).

We should add that the biochemical processes involved in the destruction of "useless" highly organized compounds differ

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[66] "We see that the structures are not static configurations, but it appears as if the molecules were going in and out, forming a dynamic equilibrium.in which the so-called fibers [the author concentrates upon the results of the mitotic spindle electron microscope study] exist as a statistical entity, not as rigid fiber, as we might ordinarily envision...We have come more and more to feeling that certain molecules or ultrastructures in cells are not just statically organized but become organized only when they are needed for specific functions. We should look at the cell machinery in a relatively simple, mechanistic manner, the way we look at the structures and functioning of an automobile or computer, for example, only for short periods of the cell life. Unlike those simpler, man-made machines, some functional parts of cells are very short lived, being 'created' or 'destroyed' according to need and following an intricate program" (Inoué, 1969/139-171).

from the biochemical processes engaged in the "de novo" production of them (Waley, 1969/150; Mahler § Cordes, 1971/488-9).[67]

The concept of a "development" or a "synthesis" is not restricted to the period of the embryogenesis alone. An adult organism, whether a bacterium or a man, might be compared to a fountain which has a relatively constant "shape" (a fan, a cascade, and so on) but whose elements are in constant movement. Let us suppose now that the shape of this fountain changes from a little microscopic spring to a colossal fan of water. This will help us to understand, in terms of molecular biochemistry, what the "developmental path" of, let us say, a mammalian limb, means.

But this metaphor is still inadequate in many important aspects. The details of a fountain, granted that they are moving, are nevertheless homogeneous, down to the level of single water molecules. The living organism is heterogeneous in its chemical details, in its sub-cellular details (nucleus, Golgi apparatus, mitochondria, lysosomes, endoplasmic reticulum, desmosomes, chloroplasts, flagellae, and so on), in its cellular details (cartilage cells, muscle cells, glandular cells, neural cells, bone cells, glial cells, and so on), and in its "organic" structures (veins and arteries, glands and bones, joints and eyes, and so on). Each "organizational" level is not only composed of the various simpler elements of the "lower" level, in various numerical proportions and in various spatial arrangements of those elements (Green and Goldberger, 1967), but at the same time each organizational level, in its whole range of variously shaped structures, undergoes the constant exchange of elements which are formed and renewed all over the life span.

> "...the individual cell as such remains recognizable similar to itself, i.e., essentially invariant, despite the incessant turnover and reshuffling of its content...small molecules go in and out, macromolecules break down and are replaced, particles lose and gain macromolecular constituents, divide and merge, and all parts move at one time

[67] Fruton (1972/401) quotes an amazing text of Magendie (1816-17/v. I, pp. 19-20) who at the beginning of the 19th century postulated a constant exchange of matter within the body and who called it nutrition. This "internal motion" was based on the process of "expelling" the molecules which are no longer needed as components of the organism, and of replacing them by new molecules.

> or another...Yet despite the absence of an orderly static frame, the various activities of all parts remain coordinated in the maintenance of the standard pattern of order in any given cell. It is an order of relations rather than of fixed positions..." (Weiss, 1961/5-7).

The developmental stage (embryogenesis) is only macroscopically, observationally the most impressive expression, manifestation of this continuous *"de novo"* formation, which, in fact, lasts until the death which immobilizes it. In a way, a dead body is like a frozen fountain. In the proper conditions it might be preserved in the structurally unchanged state during any time period, but it could not be considered any longer as a "living"body.[68]

Summing up, this closer analysis of the "hereditary trait" has led us to a rather general statment about the ubiquity and continuous pervasiveness of the "de novo" formation processes in the living body.22 But the metaphor of a fountain which changes its shape gradually and grows in its dimensions is inadequate not only because of the homogeneity of its "material." It is inadequate from the point of "functionality" of its elements. What does this mean?

3.16 The intrinsic integration of the metabolic turnover

We will discuss the problem of functionality in two steps.

First, the parts of an organism, let us say, of a fruit fly, form a sort of physical mechanism, in which the precision of each part is a physically

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[68] "We conclude [the] survey of the noninjured cell, as seen by cellular biologists, with the impression of a dynamic unity with its parts in constant motion and change...inspection of the living cell shows it to be a dynamic system; the filamentous mitochondria are continuously changing their shape, fragmenting, rejoining to form long threads, branching, forming globules along or at the end of the filament, and moving through the cell up to the nucleus and away again. The nucleoli revolve inside the nucleus and move to and from the nuclear membrane, as if drawn thence by itinerant mitochondria. The protoplasm, in plant cells at least, is in constant flow; the cell membrane of animal cells varies in the extent to which it undulates in 'drinking movement.' The chemical analysis of homogenized cells, and even the ultrastructural analysis of fixed cells, can tell little of the dynamic life of the cell, that is, of cellular biology. The chemical analysis of homogen-ates has been likened to the behavior of a man who blows up a house with a large grenade in order to see what is inside it. From analyzing the pieces he can perhaps determine what materials went to its construction and what furniture it had, but he can only surmise as to the life that was lived in that house. The electron microscopist has a totally static view vaguely reminiscent of a Victorian family photograph, with the components frozen into formal rigidity. Thus electron microscopy and conventional biochemistry must "be seen as two essential tools of cellular biology which have meaning only as partial and static answers to the complex dynamic whole that is a cell" (Chayen and Bitensky, 1973/621; see also Barrington, 1972/1-2).

necessary premise of their collective functioning. Now, if all the parts, all the chemical elements of this fly are in a constant flow, the substitution of the new details have to be precise enough to permit the continuation of this collective function.

> "Although the structure and metabolic activities of a cell are organized for its preservation, the protein components are continally being destroyed and replaced throughout the cell's existence" (Herskowitz, 1973/22; see also P. Weiss, 1965).

So the process of the exchange of the biochemical machinery; of the chemical molecules, their destruction and replacement, has to be coordinated- in some way. The elements of the fountain show no special mutual functional relationship; that is why their "replacement" does not presuppose any controlling agency (or system of agents).

Secondly, the parts of an organism are not in a functional relationship just from the beginning of a concrete, particular "life cycle." During the "developmental phase" the parts are gradually formed in such a way that in the adult form their mutual functional relationship is physically determined. The embryonic tissues are achieving their "functional" structure step by step, the limbs grow out of the completely non-functional primordia, the red blood cells develop from the cells which contain no hemoglobin molecules, the eye-lens cells develop from the cells which are not capable of producing crystalline proteins. This fact is not limited to the microscopic phenomena. Upon the molecular level of bodily organization the whole series of "precursors" (functionally inactive molecules) precedes the final appearance of the molecule of a hormone, of a contractile protein fiber, of an enzyme, and so on.

So even before the final functionality of the whole organism is reached, its parts are developing gradually in a way which physically predetermines their final dynamic cooperation. And here again, the problem of mutual integration of the developmental processes seems to be quite evident.

The individualizing hereditary traits, on the other hand, are not functional, at least upon the level of a single organism. (They may, however, play considerable role on the social level of an organism's life). But the individualizing hereditary traits are physically indivisible from

the functional, or developmental, structures of the "common" and/or "adaptive" hereditary traits (P. Weiss, 1967/821; Woodger, 1967/358ff.). The colour is physically inseparable from the eye, the shape and colour of the hair is inseparable from the hair itself and the hair cannot exist without the skin, which belongs among the basic traits (1st group). Fingerprint pattern cannot exist without the hand which is a "basic" hereditary character. So the lack of functional link between the parts of the "individualizing" phenotype does not detract in any significant way from our preceding statements on the observed link between the developmental and functional phenomena of the life cycle.

3.17 Reduction of the repair and regeneration processes to the developmental process

The permanence and continuity of metabolic turnover during the whole life cycle leads to an important observation. Traditionally, the life cycle was divided (mentally) into developmental, or embryonic, and adult, or functional, phases. Now, if during the functional adult phase virtually all structures undergo a constant destruction (catabolism) and renewal (anabol-ism), we might say that the developmental processes persist in spite of the fact that the functional state is achieved. Although the "de novo" formation of the body is not visible (in the sense in which it was macroscopically observable during the embryonic phase of the life cycle), the developmental process goes on as during the developmental phase.

Because, however, the functional (adult) state of the phenotypic structures is already achieved, the phenomena of metabolic turnover are not visible. Above the molecular level, structures have reached the steady state and the continuation of the developmental processes in the form of metabolic turnover may be detected only by special observational techniques. If, however, a local damage produces a "gap" in the structures, the developmental processes may "fill"it with new, functional structures, which in some cases is visible even on the macroscopic level. The macroscopic "gap" has revealed'the presence of the continuous developmental process, it did not release it (see Goss, 1964, 1969). If this hypothetical assumption were true, the process of the repair and regeneration would not have to be explained by postulating special regulatory, adaptive mechanisms. It might be interpreted as the manifestation of the same process which is responsible for the appearance of the whole life cycle[69] and for the continuity of the metabolic turnover.

[69] Some striking similarities are registered (Faber, 1971/127ff.).

This inference will be strengthened by an analysis of the nature of functional repetitive processes and of the notion of an anaplerotic process. This analysis will be made in the fifth chapter of our essay (see section 5.9).

3.18 The reduction of the biological phenomena to the molecular level of structures and events

As we have seen from the above evidence, the epigenesis and repetitivity of biological phenomena are not less impressive on the biochemical level of bodily organization than it is on higher, cellular or organic, levels of this organization. Because of the essential repetitivity of molecular events within the cell, their detailed description becomes possible, and in fact, even in vivo electron microscope observations reveal a non-random pattern of movements and changes on the level of greater molecular complexes (see Rebhun, 1972). This direct evidence is further strengthened by the results of indirect observations and calculations (Tyler, 1973/122; Yost 1972/119; Ord et Stocken 1973/171). The modern view on the nature of the living cell is basically dynamic, and the traditional opinion about the random arrangement of the chemical compounds in cytoplasm was shown to be wrong.

> "Typically, in living systems, important microscopic fluctuations are generated by microscopic machines whose sequence of states is not random. We should not be prevented from studying the macroscopic effects of submicroscopic activity by adherence to the traditional postulate of statistical thermodynamics, that all microscopic variables are random and that all machines are macroscopic" (Kornacker, 1972/9).

3.19 On the observational irreducibility of the epigenetic phenomena

As we shall see in the next chapter, the functionality of biochemical processes is conceptually equivalent to the functionality of such macroscopic devices as the optical system or the musculo-skeletal locomotory system.

> "There is no dividing line between structures in the molecular and in the anatomical sense: macromolecules have structures in a sense intelligible to the anatomist and small anatomical structures are molecular in a sense intelligible to the chemist ..." (Medawar , 1967/105).

The repetitive "de novo" appearance of biochemical machinery within the cell is thus as intriguing as the "de novo" appearance of an adult elphant's body is. The question-raising evidence is the same in macroscopic and in the microscopic, molecular aspect

of the living body. The postulate of conceptual reduction of macroscopic evidence to the level of molecular evidence (Kuhn, 1962; Feyerabend, 1962; Caws, 1965; Pallade, 1965; Dobzhansky, 1969; Schaffner, 1967, 1969) changes nothing in the nature of the main problem which intrigues us. Hereditary transmission of biochemical structures does not seem to be less mysterious than the transmission of macroscopic, anatomical properties. But in a way, the postulate of reduction forces us to construct in our minds the extremely complex four-dimensional non-random replica of a cell, or an organism. The number of details, structures, heterogeneous events which appear upon the biochemical level exceeds by several orders of magnitude the heterogeneity of relatively crude and imprecise ideas "based upon macroscopic observations. The descriptive reduction, in other words, amplifies the question-raising evidence, instead of reducing it.[70] The postulate of genotype, which was invoked under the impact of the macroscopic, relatively imprecise and relatively simple evidence has now to explain causally the astronomical number of structural and dynamic details recognized on the biochemical level of life.

3.20 The concept of the epigenetic event

The preceding analysis of the "life cycle" concept, of the "developmental path" concept and of the metabolic turnover concept has served to prepare some empirical evidence for the elaboration of the precise and more generalized notion of epigenesis.

The epigenetic events constitute the main observational question-raising evidence which provoked the origin of the "phenotype-genotype" distinction. It is essential now to have a clear, unequivocal understanding of the essential and relevant (from the theoretical point of view) elements of this concept.

These essential elements seem to be as follows:

a) Epigenesis is an event, not an a-temporal state. Its most basic property lies in the change from a less complex to a more complex structure. Consequently, an epigenetic event cannot be described in terms of a single structure, however complex. Two

[70] "If the assumption [about the reduction of life to the physical elementary particles] is true...the whole development of life, intelligence, society, etc....can in principle eventually be explained by referring it to an ever more complete knowledge of the properties of these basic molecules... these conclusions, however, all fall to the ground if it turned out that natural processes...contain a really creative movement, in which there appear new orders and orders of orders..." (Bohm, 1969/29).

different structures, at least, constitute the minimal descriptive evidence for an epigenetic phenomenon. These two different structures, or states, cannot be conceived as coexistent. If that were so, the dynamic element of the epigenesis would vanish, and the two structures could be reduced to an a-temporal state.

b) The two above structures have to be really different from one another. By "really," we mean "physically." So the concept of epigenesis implies the concept of physical change. If it were not so, epigenesis would not provoke any need for a causal explanation.

c) The two structures are not only different from one another, but one of them is more complex than the other.

d) The two structures are observed to appear in a 'temporal ordter such that the less complex precedes the more complex.

Epigenesis means an increase in complexity. But how can complexity be measured? Which entity is more complex and which is less complex? Before we try to formulate a more general concept of an increase in complexity, let us consider a concrete epigenetic process such as production of protein molecules.

3.21 The notion of the change (increase) in complexity

The majority of proteins is made up from twenty different, "basic" forms of aminoacid molecules. The single molecules are linked together by the so-called peptic bonds, so that a long chain (polipeptide) is formed, in which different forms occupy a certain position (sequence position). The properties of a given polipeptide chain, which quite often is more than 100 aminoacid molecules long, depend on the sequence of different aminoacid molecules within the chain.[71] (See Figs. 7.3, 7.4 and 7.7).

What does it mean when we say that "a given polipeptide chain is

[71] 5 Since Sanger started the techniques of establishing the sequences of amino-acids in proteins, the results obtained have completely established that proteins are well-defined molecules composed of peptide chains with unique sequences. The number of these known sequences is increasing every year (Florkin, 1972/293). The yearly published Atlas of Protein Sequences and Structure (Dayhoff, ed.,) contains the growing number of newly-established structures of proteins which constitute the major group of macromolecular constituents of living bodies.

more complex than the random set of single, 'free' aminoacid molecules which might be obtained by the destruction of its peptide bonds"? It means that from the same pool of "free" aminoacids we might obtain a completely different sequence, the polypeptide chains showing completely different properties and that the number of these different possible polypeptide chains obtainable from the same pool of aminoacids is extremely high.

In fact, from a hundred free aminoacid molecules representing twenty different forms of them, we might obtain 20^{100} forms of polypeptides.[72]

In more general terms, then, an increase in complexity means a change towards an integrated structure composed of parts which, as such, were not intrinsically determined to form this particular structure, but might, in principle, form a greater number of different integrated structures.

In the same sense the fantastic figures, "feathers" and other configurations of crystals iced in winter on the window illustrate complexity of structure. It is quite obvious that the same number of water molecules might be arranged in many different configurations. So the complex structure taken as a whole demonstrates only a small fragment of the structural potentiality we recognize in its parts taken as a set of separate, individual units.

The epigenetic change as such does not seem to provoke any particularly difficult causal interpretation. The patterns observed in the inanimate world are often very complex and they may serve as the illustration of true epigenetic phenomenon. What does create the'problem is the repetitivity of this phenomenon. The pattern of the ice crystals on the window is not repetitive. The complex pattern of bodily structures, even in the case of the sim-pleast living organisms, is complex and repetitive at the same time. And this

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[72] "The number of possible proteins of the molecular weight 60.000 (human hemoglobin has the m.w. 65.000, yeast alcohol dehydrogenase has the m.w. 140.000) is 10^{625} . This means that if the entire observable universe were packed with protein molecules, each one different, and if each of these have changed into a different one every second since the sun started to condense from interstellar gas, not every possible protein molecule would yet have existed, by a very large margin" (Pringle, 1963/15). We should add that the estimated number of all the different kinds of protein molecules which are recognizable in living bodies is probably less than 10^4 and almost absolutely certainly less than 10^5. Of course, we are talking about the functional protein molecules, not about the protein antigens, although it may be that the configuration of a protein molecule plays a significant role in its antigenic properties. The configuration of the protein molecule, in turn, was not included in Pringle's calculation. A protein molecule of a given sequence, let us say, of 149 aminoacids, may have roughly speaking 4^{149} to 9^{149} different conformations in solution (Anfinsen, 1973/228). "It is important to stress that the amino acid sequences of polypeptide chains designed to be the fabric of protein molecules only make functional sense when they are in the three-dimensional arrangement that characterizes them in the native protein structure" (i.e., *in vivo*)(Anfinsen, ibid.).

does provoke the question of the origins of this repetitivity.[73]

The complexity of a single polypeptide chain of the major extracellular nuclease of Staphylococcus aureus, with respect to the random set of free aminoacids into which it can be broken down, may be expressed by the relation 2800:1. If the Staphylococcus nuclease is repetitively formed from the random set of aminoacids, and all the other, incredibly numerous polypeptide forms are not, we have to postulate some physical constraints which will be able to control the process of the Staphylococcus nuclease production with the utmost physically possible precision.

The hereditary characters in the living body are all produced by the epigenetic process. And all of them reveal a striking repetitivity which is not less pronounced on the biochemical level than it is on the higher levels of bodily organization.

The repetitive appearance of complex structures from among the homogeneous, or less complex, may, in turn, be rephrased in terms of the adequate restrictions. These restrictions have to be postulated in order to explain the strange lack of other complex structures equally possible from the point of view of possibilities inherent in the simpler state. In other words, the repetitivity of one particular complex state is the manifestation of a sort of probabilistic deficit.[74] The problem of epigenesis in the case of living bodies amounts to the explanation of the constraints which restrict the increase of complexity in such a way that the resulting complex structures are strictly identical.

3. 22 The question-raising nature of the repetitive epigenetic phenomena

We might rephrase the question-raising element of the repetitive epigenesis in this way. The final, complex structure which arises as a result of

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[73] "It is a recognition of some regularity (or recurring pattern, or order)— which makes us wonder and ask 'why?' " (Hayek, 1964/333).

[74] According to Ephrussi (1970/19) the problem of cellular differentiation (epigenesis) may be identified with the problem of "restriction." Bogdanski writes: "D'une manière générale on peut affirmer que les lois de la biologie reposent sur une structure d'interdictions immanents à chaque niveau dimensionel ce qui exclu la probabilit d'un hasard au niveau d'un phénotype" (1972/24).

the epigenetic process is composed of parts which previously were not determined to this particular structural form. They were able, according to the external determinations, to form one of innumerable integrated complex structures. So the parts alone do not provide us with the explanation of why this particular form was synthesized. If this form had appeared only once, we might attribute its origins to the random set of external determinations. If, on the contrary, it reappears again and again, the external determinants cannot be considered as random any more. They have to be conceived as repetitive, too.[75]

The epigenetic nature of the hereditary phenomena does not allow us to accept any explanation based on the re-description of the earlier stage (Coleman, 1971/42). For the earlier stages, being less complex than the later ones, are not intrinsically determined to a particular more complex form, but to a greater number of them. That is precisely what is meant by the notion of the increase in complexity, or heterogeneity.

The repetitive epigenetic phenomenon cannot be causally reduced, either to the intrinsic determinations operating within structural parts of the entities involved in this event, or to the earlier structures preceding the appearance of the more complex ones.

Summing up, the hereditary phenotype cannot be causally reduced to its own *redescription.* The postulate of an adequate causal agency seems necessary. This agency, as we already know, is called genotype or genome. Before we pass to the analysis of this agency, we shall discuss another aspect of hereditary phenomena, namely the *integrative* epigenesis.

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[75] Blandino (1969/320ff.) uses the analogous argumentation in reference to the phenomena of evolution. He calls for the admission of the existence of "preferential laws favouring living structures."

CHAPTER FOUR

PHENOMENA OF LIFE - FUNCTIONAL EVENTS

4.1 The problem of the relationships between the coexistent parts of the phenotype

From the preceding discussion of phenotypic, hereditary traits we have grasped two important general ideas which will determine the direction of our further analysis of phenotype reality. First we have seen that every, however arbitrarily separated, hereditary element of the 'life cycle appears "de novo" as a result of a dynamic process we have called the "developmental path." But we have also realized that some hereditary traits, although remaining in a dynamic state because of the metabolic turnover, do not enter into dynamic relationships with other elements of the life cycle. While the nerves, muscles and bones, for instance, constitute a set of different but dynamically correlated phenotypic traits, the pigment granules in the eyes, the pigment granules in the skin, the fingerprint patterns, the antigens and other characteristics belonging to the "individualizing" (third) group of phenotypic traits do not enter into dynamic mutual relationships, either between themselves or with the structural elements of the organism in which they reside. The hereditary phenotype may, then, upon any arbitrarily selected stage of its time dimension, be divided (mentally, conceptually) into parts which are coexistent and dynamically interdependent, on the one hand, and into parts which are coexistent but dynamically independent, on the other. The first category of parts is commonly referred to as functional. But the nature of this specific dynamic relationship is the object of controversial interpretations, to the extent that even the purely descriptive notion of function is virtually lacking, which, of course, creates a basic obstacle in the progress of understanding of this phenomenon.

A close dynamic relationship between the activity of neural cells and the activity of glandular cells, between the activity of neural cells and the activity of muscle fibers, between photosynthetic processes and the processes of a growth and reproduction, between the activity of mitochondria and the flaggellar movements and so on, is quite obvious. This sort of dynamic relationship is called functional. But the precise nature of this sort of relationship is still not clear.

It is not clear, firstly, whether so-called functional events are purely physico-chemical, and, secondly, how it is possible that many obser vationally

completely different events are all labeled by the term "functional." What, then, does this term mean exactly? Would it be possible to abstract a common trait characterizing all these different forms of dynamism? If so, does this common trait represent a sort of objective property? We will have to investigate some concrete examples of so-called "functional" relationships in order to find the answers to these questions.

4. 2 Some general problems implied by the concept of function

The discussion of the concept of function is extremely difficult for several reasons. First of all, those biological processes which are most commonly referred to as function, as, for instance, digestion, defense, locomotion, excretion and so on, are extremely complex, and detailed spatial and temporal descriptions of them are still far from being complete. These processes are quite evidently dependent upon the nature of biochemical molecular events. To understand the nature and "function" of intracellular respiratory processes, for instance, an extensive study of biochemistry is necessary. This, of course, puts a certain limit to a discussion of the problem of function by professional philosophers.

Secondly, the problem of functionality in the mind of philosophers and of biologists as well is closely related to the problem of purposiveness. This in turn leads almost inevitably to the allegedly dangerous and "vitalistic" way of thinking. Why are these ideas so dangerous, one might ask. The reason is that vitalism is essentially a dualistic doctrine. Monism, on the other hand, seems to be an official ontological doctrine of contemporary biology. As Woodger rightly observed:

> "The desire for monism...is of course operative in the objections to vitalism in biology. In the vitalism of Driesch an appeal is made to a special kind of agent which is only operative in living organisms...Probably the average biologist never troubles to analyse his objections. His 'scientific intuitions' revolt against it. He 'feels in his bones' that something is wrong, and that is enough" (1967/205. See also Schubert-Soldern, 1962/10, 18, 22).

Until the last decades, analyses of the nature of functional processes were usually limited to the macroscopic level of its reality. The more fundamental, molecular phenomena constituted a sort of "black box." Since the notion of function was conceptually inseparable from teleological, and consequently vitalistic, ideas, some authors were persuaded that this whole set of ideas flows from an ignorance of empirical data. Kantor, for instance, writes:

> "The teleologists stress the difficult features of biological events and trade upon ignorance of details" (1962/246),

and Crick, attacking vitalism, writes:

> "The life is mysterious only in proportion as one is ignorant of molecular biology" (quoted after Dix, 1968/338).

In our analysis of functional events we will have to carefully avoid this possibly justified accusation. The analysis of functionality in terms of molecular biology was never made. Without an appropriate analysis of molecular "functional" events we cannot judge whether the opinion of Beckner (1959), Nagel (1961), Ayala (1972) and Wimsatt (1973), who claim that functionality is reducible to purposiveness is correct and what the conditions of this reducibility are.

Still another difficulty arises from the fact that many authors, without entering into analysis of the term, or of the processes supposed to be characterized by their "functionality," believe that the evolutionary process, and natural selection in particular, provides a correct and adequate explanation for the existence of functional events in living bodies.

Simon describes the origins of the above postulate in the following way:

> Modern biology, of course, disdains explanation in terms of the wishes of a designer or creator — On the other hand, the biologist is... concerned with the creation of how the organism came to possess that [functional - PL] feature, or rather, how there came to be a species whose members bear that feature. It has been this consideration that has led to the attempt to define biological function in terms of evolutionary theory. Thus Canefield has proposed an analysis of function statements in biology according to which a specification of the function of a particular structure or process is equivalent to indicating how that feature is useful to its possessor, where "useful" is defined in terms of contributing either to the preservation of the life of the thing that may have it or to the maintenance of the species. What may look as though it were created by a designer with a purpose is thus explained as a consequence of nonteleological processes of natural selection of the results of random variation among the progeny of ancestral types. Those biological structures that have functions have them because the organisms in which they occur are the descendants of organisms whose ability to produce fertile offspring was dependent upon possessing those structures (1971/77-8).

Caspari alludes to

> " … the postulate that biological processes should be described at the molecular level. The implication is that if'a process has been completely described at the molecular level, there is nothing else to describe it...It still leaves open, however, the problem of function, and how we can account for it...Function must be understood as a consequence of natural selection.

> The question of the function turns out to be basically a historical one, the question of the origin of stabilising mechanisms in the history of the species..." (1964/143).

Similar opinions may be found in Ayala (1970), Schaffner (1969), Cowden (1972), Pattee (1969), Waley (1969), Kantor (1962), Bonner (1963), Felter (1965). Even if it were essentially true, we still do not know what the term "function" actually means.

One might ask here how the problem of the correct understanding of *functionality* is linked with the problem of the distinction between the phenotype and the genotype. The answer is this. At first sight, the so-called "functional" relationships postulate a special form of structural relationships within the phenotypic structural pattern. Now, if the notion of "functionality" does not represent any *objective* property of the phenotypic structures, then the so-called "functional" relationships do not enter into the *objective* notion of phenotype. Consequently, the repetitivity of epigenetic phenomena in separate, unrelated developmental paths constitutes the only empirical element to be explained by the postulatory genotypic agency. If, on the other hand, the "functional" relationships between at least some phenotypic structures represent an objective descriptive category, then the postulatory genotypic agency should also explain their repetitive epigenetic origin.

The existence of a true, objective relationship between heterogeneous elements constituting a phenotype (a set of phenotypic traits) introduces the idea of *objective integration* within the complex spatio-temporal phenotypic pattern. The problem of the nature and objectivity of a functional relationship amounts to the question as to whether the genotype should be conceived as an *integrative* agency and as to what are the objective limits of its integrative activity.

4.3 Some explanations on the methodological principles of our analysis of "functional" relationships

The problem of.the nature of biological function happens to be, unfortunately, connected with some metaphysical and epistemological controversies, which to the considerable extent have obliterated its primary, empirical meaning. We will have, then, to discuss briefly our approach with respect to these theoretical complications before we can start the analysis of

"functional" phenomena.

We will not enter into the details of the long-lasting controversy between mechanism and vitalism, between deterministic causalism and physical indeterminism, between reductionism and emergentism. These controversies have been reviewed again and again, and a discussion of opinions does not seem to be the correct way of solving a problem which supposedly has its roots in the observational evidence.

In an effort to disentangle the complex mesh of ideas, we will make the following preliminary assumptions:

1) We will assume provisionally that functional biological events constitute only a restricted group within the greater and more variegated set of dynamic events which are observable within a living body. In this way we will not be forced to find a general, abstract idea of "function" which would be applicable.to any dynamic event recognizable within this body. Our attention will be restricted to those events which are considered as typically functional. We will not be afraid to recognize as functional that type of dynamic event which is not applicable to the whole empirical evidence concerning phenomena of life.

2) We will assume provisionally that a functional event is not necessarily "purposeful". The conceptual reduction of functional to teleological events, in fact, creates two apparently insurmountable difficulties, both of epistemological origin.

a - The first may be illustrated by Simon's analysis of the concept of functionality (1971/81ff.). Once functionality is reduced to purposiveness, the notion of function is defined not as an immanent property of the object under study but by reference to something external to it. The final result of this reasoning leads to the Kantian "aprioristic" idea of function, as it is explicitly stated by Simon himself: "The conclusion we have drawn is basically a Kantian one: the concept of function is not derived from the phenomena we experience but is rather imposed upon them as a necessary condition for the possibility of experiencing them as comprehensible." (1971/83).

b - The second difficulty comes from essentially the same root but manifests itself in a different way. At first there is a problem of finding the right point of reference for the non-subjective definition of purposefulness. Then, however, a deeper metaphysical obstacle appears which may be illustrated by the following text:

"The endocrinologist knows that the concentration of thyroid hormone in the human blood-stream is exquisitely regulated by feedback inhibition of the secretion of thyroid stimulating hormone by the anterior pituitary gland; and it is plausible enough to assume that this feedback inhibition was developed for the purpose of regulating the concentration of thyroid hormone to which the body's tissues are exposed./.But is it purposeful?—And what about naturally-occurring inanimate systems? Do they exhibit feedback only if we believe in a Creator whose every design is supposed to have some purpose? Questions such as these have no logical answers, and hence no legitimate status in science" (Riggs, 1967/379-80).[76]

Riggs is jumping to conclusions without a proper analysis to what extent and why, if at all, the functionality of feedback structures and dynamics is necessarily linked with the process of purposeful design. Perhaps it is so, perhaps not. But anyway, the problem can be rationally investigated step by step, without premature worries or prejudices.

3) We will not be afraid of discovering eventually that functional events may be defined in pure physico-chemical terms. Wimsatt, for example, discusses among many other meanings of the term "function" the "consequence" function. He deliberately discards this form of the concept from his further analyses, for he considers it as nothing more than a synonym for "causal operation." He admits that in this sense "All the consequence of [an] operation are functions. ..without regard to their usefulness for some purpose or effect from some perspective" (1973/4-5). Wimsatt"s "consequence" function is thus a pure purposeless dynamic category. From the reductionist point of view, it is an obvious advantage. But it does not necessarily decide about the failure of the anti-reductionistic

[76] Noll, describing the model of the DNA-dependent protein synthesis, writes: "the model--although admittedly somewhat naive, nevertheless allows us to assemble a heterogeneous body of observations into a meaningful and logically consistent picture...Yet what I find most convincing, I must confess, at the risk of sounding heretical, is the compelling logic of the design in regard to the intended function" (1965/104). Noll quotes W.H. Anden (1965/18-19): "This means, of course, reintroducing the notion of teleology, for a long time now a dirty word with scientists, but they will get over the shock."

> idea of the organism as a whole. First, as we have stressed before, it is not quite certain whether all the forms of dynamism observed within the living body are really functional. Then, even a purely causal, in the physico-chemical sense, operation may reveal properties which provoke a special question about its intrinsic organization, or about its origin; and, consequently, may be causally irreducible to those forms of causality which operate within the mineral world.

We are not trying, of course, to explain away the idea of "purposiveness," or to dismiss the validity of teleological explanations in biology. In fact, we will show that this particular, specific form of dynamic causal relationship called function is determined by the epigenetic, or developmental processes, which may be called "purposeful" precisely because they are preparing the necessary structural conditions for the appearance of the functional causal dynamism. But we will try to show that the two processes are not identical that, on the contrary, they are irreducible one to another. In this way, the "purposefulness" of developmental events has a concrete system of reference, namely, a concrete, observable functional process. Our thesis is exactly opposite to that of Simon, which he has put in the following words:

> "Since the function of something is not the same as its effect, it must be acknowledged that a functional relation is not the same as a causal relation, although it necessarily includes one. The difference is that a functional relation is always either a three-termed relation, involving a structure or process, a process to which it contributes, and a system in which the other two elements occur, or a two-termed relation between the functional item and the system as a whole, whereas a causal relation is always a simple two-termed relation between two events." (1971/81; see also Wartoffsky, 1968/352).

Our analysis is an attempt to consider the same evidence from the opposite side. Simon's approach seems to be this: If the function is purposeful to the processes of development and of survival of a living being, and if this last process has no purpose whatsoever, then the process of function ultimately has no purpose either - so the notion of the function is not necessary at all in the process of giving an account of the objective state of affairs.

Our approach will reverse the order of speculative consequence. If a living animal, or any other being, *is* functioning and the developmental events are purposeful with respect to the fact of this functioning, then both concepts

are necessary if one wants to give a full account of the events which take place in the living organism.

Of course, the whole idea is dependent on the outcome of a careful analysis of the dynamic processes which we encounter within the sphere of the living body. Is it possible to find *descriptive* properties of the processes called functional which would distinguish them among other equally causal processes? Are these observational properties determined by the physical outcome of the developmental processes? If that were so, the developmental process would achieve an objective, non-arbitrary criterion-trait which would help to distinguish it from other non-developmental events. At the same time, the genome's activity responsible for the appearance of the developmental events would achieve a new role, namely, that of an integrating agent.

4.4 General considerations concerning the correct selection of empirical evidence for the study of "functional" relationships

Usually some events are called functional, and others, on the contrary, non-functional. A great many pathological phenomena are commonly referred to as non-functional. But there is a clear link between the functionality of events and the functionality of structures. We may say that an event was non-functional, but we usually blame a concrete structure. The perception of sounds may be imparied, and we will tend to say that the ear has become non-functional. A biochemical reaction may be arrested, or changed in a "non-functional" way, and we may blame the "non-functional" structure of some specific protein molecule, its "non-functional" folding, for instance (see Anfinsen, 1973/224, 227).

We will have to investigate both the dynamic and the structural elements of functionality, but because, on the observational level, any dynamic state necessarily implies a structure or structures but not vice versa, we will concentrate our attention upon the dynamic events.

The dynamic states we may observe within the living body are reducible, in the sense just explained, to movements, changes, syntheses, lyses, influences. But usually the term "functional" is used, at least on the macroscopic range of the observational scale.

Now, our problem is this. Is it possible to replace the term "functional" in its primary, dynamic sense, by other dynamic concepts used in the physical sciences? Or, to put the problem in a more concrete way, would it

be correct to eliminate the concept of "function" from a description of the life processes? In the context of the above question, we should remember that in the surroundings of the organism, the movements, changes, influences, syntheses, lyses are taking place continuously. They are never referred to as "functional." Yet they are observed on the same range of the observational scale as they are within the organism itself. So the reluctance to use the term "functional" with respect to them cannot be based on an awareness of their detailed, chemical structure. On the other hand, the textbooks of biochemistry are not less loaded with the term "functional" than those of physiology.

Is the term "function" referring to a new sort of reality, an irreducible form of the dynamic state? We have to agree that there are different forms of the dynamic state; movement is not the same as change, synthesis cannot be reduced to a lysis. And yet some movements, some changes, some syntheses or lyses observed in the sphere of living organism are called "functional," while in pathological conditions some syntheses or lyses, some changes occurring on different levels of bodily organization, are called "non-functional." What, then, is the criterion of distinction between the "functional" and the "non-functional" dynamic processes in the body?

We will try to solve our question in the following manner. We will select an example of the dynamic state which is generally described in terms of "functionality." We will try to understand which aspect of the selected phenomenon is called "functional" and what that means in this particular concrete case. Then we will try to realize how the "functionality" of our phenomenon is dependent upon the developmental phenomenology. In that way we will investigate the relationship between the development and the function. If function is discovered to depend upon developmental epigenesis, we will gain non-arbitrary criteria for determining to what .extent the phenomenon of "functionality" constitutes new and relevant "question-raising" evidence, which has to be solved by the postulatory genetypic agency.

Let us start our analysis.

4.5 The ease study — locomotory movements of the spermatozoon

As an example of the apparently "functional" dynamic state, we have selected the process of fertilization.

> "...The fertilization in animals is a complex process involving the fusion of the spermatozoon and the ovum...Fertilization...has a dual function:
>
> (1) to cause the egg to start developing, and

(2) to inject a male haploid nucleus into the egg cytoplasm..." (Berill, 1971/217).

"...the sperm must find the egg and unite with it...[it] moves by means of a tail whose great structural complexity has been revealed by the electron miscoscope. An energy supply permits this mechanical movement, which can be turned off or turned on and controlled by particular environmental influences. It [the spermatozoon] contains energy rich substances and the appropriate metabolic enzymes..." (Kühn, 1971/133).

"...The movement of flagella [the spermatozoon's tail is an example of such a flagellum - PL] commonly involves the generation of waves that are transmitted along it, either in a single plane, or in a corkscrew pattern..." (Harrington, 1972/45)

The tail of the spermatozoon is built up from ten sets of tubules, nine of which are arranged into a cylinder 0.15-0.2 micron in diameter, while the tenth, composed of two tubules, is found in the center of the cylinder. The exact detailed structure of the tubules and of the many other elements contributing to the structure of the tail (second fibres, for instance) is not known. But the evidence available suggests that the tail is not a passive organ, because some cilia or flagella that have been detached and isolated from the cell can beat if ATP is added to the suspending medium (see Novikoff and Holzmann, 1970/143). Now ATP[77] is produced by the inner membrane of mitochondria. "Mitochondria...are wrapped around the flagella responsible for movement of sperm cells" (Novikoff and Holzmann, 1970/104; see also Tyler, 1973/114).

"In most of the cells where cilia or flagella occur their primary function is obvious: they move back and forth like ours. When attached to a movable, boatlike object such as a protozoon [or in our case a spermatozoon -PL], they propel it through the liquid around it..." (Satir, 1961/53).

The above quotations were collected here in order to give the reader a sample of the concepts used to describe phenomena which are either observed directly or else reconstructed from the data registered through

[77] ATP (adenosine 5'-triphosphate; see Fig. 5.5) in the presence of a specific complex protein molecule, (total molecular weight 280.000) composed posed of several probably non-identical sub-units, all of molecular weight about 25.000, and in the presence of the Mg*+ ion, undergoes a rapid hydro-lytic breakdown to ADP (adenosine 5'-diphosphate) and a single phosphate group. This hydrolytic process .yields a relatively high amount of energy (ca. 7 kcal/mol ATP).

The majority of energetically "unfavorable" chemical, electrical or mechanical events which occur in living organisms are coupled with the hydrolysis of ATP, and the energy released is transferred into those "unfavorable" events.

electron microscopes.

> "Perhaps the most remarkable part of these investigations is the correlation they reveal between the form [structure -PL] and function..." (ibid.) "Cellular structure, down to its minute details, remains constant as long as function is constant. When the structure of an organelle [mitochondrion, nucleus, cilia, Golgi apparatus, lysosome, endo-plasmic reticulum—and so on -PL] changes from one type of cell to another, the difference usually corresponds directly to a change in its function..." (ibid. See also Porter, 1963/121, 145).

The "physical" "mechanicistic" sense of this observation is quite clear. The dynamic state, called function, is strictly determined by the structure of the organelle. The mitochondria produce ATP because of their structure, for they contain a complicated system of enzymes, arranged in such a way that the production of the ATP becomes physically inevitable. Mitochondria are localized close to the specially structured flagellum, so that the ATP inevitably produces the movements of the flagellum. This inevitability is purely physical and it means nothing more than the physical inevitability of the movement we can observe in a watch which is properly wound. In the same sense a tree bends inevitably under the impact of a storm, or water splashes under the impact of a stone falling down into it. All these dynamic events are observable in their details. We may for instance try to observe the balance of the watch, or the splashing water under an electron microscope and we may use high-speed cinematography in order to break down any of those dynamic states into their minute details. But the essential question remains: is the locomotory movement of a spermatozoon a "functional" event, in a sense in which the bending of a tree during a storm is not? Rocks do not bend during a storm, and we know why - their structure is such that they cannot. So would it be correct to say that the structure of a tree is functional with respect to the bending during a storm? Or let us take another example. The moon pulls the water in the oceans in a rhythmic, repetitive pattern. The gravitational influence of the moon is not restricted to the water, in the same sense in which the storm does not selectively influence the trees.

But rocks do not yield to that influence, as they did not yield under the impact of the wind. Now, if we turn back to the spermatozoon, we

may realize that the mitochondrion's activity, or the ATP's energy, is used exclusively or almost exclusively to drive the tail's locomotory movements. It seems precisely because of this selectivity, in which the ATP production is coupled with the movements of the sperm tail, that the ATP production is called "functional." In what sense is this selectivity to be understood?

4.6 The restriction of energy flow — the presumably characteristic property of functional events

This selectivity might be explained in terms of the structural constraints which direct the "stream" of energy in space and control its release in time. But is it a sufficient criterion to distinguish the presumably "specific" "functional" phenomena from "non-functional" ones?

The restriction of energy flow, so common in the processes going on within the sphere of the living body, is also not uncommon in the world of mineral, non-living matter. Rivers run energy down to the sea, and this constant current of energy is restricted to the riverbed. The energy stored within the hot center of the earth flows out on the surface through the few holes which we call volcanoes, and again this flow of energy is restricted by the configuration of the rocks which form the outer coat of our planet. The energy of the sun, on the other hand, flows into "outer space" in an unrestricted fashion, and it takes the rather complex structure of the chloroplasts in the leaves of plants, to restrict this energy, both in space and in time, and to make it functional.

The examples of a river, or a volcano, have shown that the restriction of energy flow alone is not a sufficient criterion for distinguishing between "functional" and "non-functional" dynamic states. Is it possible to recognize some other characteristics of "functionality"?

Let us take another example in order to gain a deeper insight into the nature of functional events. A safe hidden in the basement of a bank may be opened in many different ways, including, say, the use of explosives. But there is, when we take into consideration the concrete structure of a particular safe, a physically minimal (in terms of energy) way of opening it, namely, using the right key and turning it in the right direction. Though explosives may turn out to be equally effective, they do not only open the safe but at the same time provoke many other physical effects, including a terrible noise. If one uses the right key and if one handles it in the proper way, the only physical effect of the activity will be the

change in the position of the closing bolt. This means that the doors of the safe will be open. All other physical effects will hardly be noticeable. For the structure of the locking mechanism, the structure of the key, the lubrication of moving parts, and the amount and direction of pressure exerted, or work done, will constitute the physically minimal set of conditions which were required to move the bolt from the position "closed" to the position "open." If, on the other hand, the locking mechanism was rusted, if it was not lubricated properly, if the pressure exerted on the key was excessive or not directed properly, then the bolt perhaps would move into the position "open," but several other physical changes would occur too. An amount of heat produced because of friction, would be liberated, some scratches on the surface of the key or on the parts of the locking mechanism would remain. We could imagine a situation in which, because of the wrong shape of the key, because of the wear of the locking mechanism, or because of other similar factors, the proportion of work put into the movement of the bolt would be relatively small in comparison with the work used to produce other physical effects in the surroundings. In this case the whole event would be proportionately less "functional."

The concept of the physical influence includes ineffective, just-effective and over-effective forms of the physical interaction between the bodies. The ineffective ones produce heat changes only without producing any intrinsically irreversible changes in the influenced bodies. The over-effective ones produce both the intrinsically irreversible changes in the influenced bodies and a greater than minimal amount of thermal energy. The just-effective ones we have called the functional events. An ineffective attempt to push a wardrobe may serve as an example of an ineffective physical influence. But if we prefer something more learned, we may turn our attention to the myasthenia gravis syndrome, to the cardiac inefficiency syndrome, to the hypoacidity syndrome, to the myxoedema syndrome, or to others of the innumerable forms of functional disturbances, all of which are examples of physical influences which are ineffective. On the other hand, a bomb explosion is an example of an over-effective physical influence, because the military useless damage is here quite obvious. In the living organism, phenomena such as pathological convulsions, hyperacidity, hyperthyreosis and so on may serve as examples of over-effective physical influence.

We should note here that in the case of the explosives used to open the safe, the "functional" situation is absolutely inconceivable. It would be physically impossible to place a bomb in such a way that it would move the bolt alone without producing other physical events.

Now, let us rephrase the above analysis in terms of biochemical reactions.

4.7 The analysis of "functional" events on the molecular level of the phenotype

The macroscopic dynamic processes observed within the living body are the manifestations of the chemical processes in which energy is transferred from one molecule (or a set of molecules) to another. An amount of energy absorbed by a molecule may, in principle, produce in it three different effects.

a) The amount of the absorbed energy may be so small that no irreversible change will be produced within the molecule, and the temporary surplus of energy will be dissipated through collisions with the surrounding matter. A local increase of heat will be registered, but the amount of energy absorbed and then dissipated will not be recoverable from this sytem. We will say that the free energy of the system has decreased (see Yost, 1972/130).

b) The amount of the absorbed energy may be so great that both irreversible change will be produced within the molecule and some surplus energy will be dissipated in the surroundings.

c) The amount of the absorbed energy may be just sufficient to produce an irreversible change within the molecule. In this case, practically no energy will be dissipated in the surroundings .

In case c), the amount of energy absorbed by a molecule was *"minimal"* with respect to the irreversible change produced by it. No heat was produced in the surroundings, no energy was dissipated. The increase of entropy of the system (ΔS) although inevitable, was minimal.

Case a) is *causally ineffective.* The energy transferred from one entity to another is too small to affect the influenced entity, a molecule or a molecular complex, in an irreversible way, so that the original equilibrium will be achieved sooner or later by a spontaneous and inefficacious dissipation of energy.

Consequently, the biological, or, more precisely, the biochemical, dynamic events cannot be reduced to the first kind of energy transfer. But there are serious reasons and an impressive number of empirical data which may lead us to the conviction that the second form of energy transfer is also not typical of the phenomena of life.

The first reason which forces us to admit that practically no surplus energy is dissipated in the surroundings while biochemical reactions take place follows from the observation that these.processes occur in isothermic conditions. The amount of work which is done during the organic syntheses, during the locomotory movements, and other physiological events is great[78] and the temperature changes observed in the living body are rather insignificant. The efficiency of biochemical reactions must then be close to the maximum allowed by the fundamental laws of thermodynamics. A one hundred percent effective transfer of energy is physically impossible, but the loss of energy in the living body is close to the physically possible minimum. Because the effectiveness of biochemical reactions is beyond any doubt (in non-pathological conditions, of course), it seems that the majority of biochemical processes consist in transferring just the effective, and still minimal, amounts of energy.

The second reason is founded upon the observation that many biochemical structures of the living body are relatively labile and unstable. The "energy-barriers" which keep them in the equilibrium required for the successful performance of their task might be easily destroyed if a significant amount of energy were dissipated in the surroundings of these structures. So either we have to postulate special "forces" which prevent them from decomposing, or we have to admit that there is no significant superfluous energy present in their environment.

Finally, calculations based on observations of photosynthetic processes, calculations concerning the energy transfer in the so-called "coupled reactions," and many similar facts, provide a fragmentary but consistent evidence for the claim that the dynamic processes of life are physically efficacious and minimal at the same time.

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[78] "Even in a small procaryote cell such as the colon bacillus *[E. coli]*, the energy requirements, as shown by the ATP turnover, are impressive. At least two million ATP molecules are broken down per second in order to achieve the biosynthesis of all the cell components" (Berill, 1971/29).

4.8 Economy, "minimality" of energy transfer during functional events and the specific structural relationships of a functioning system

Now, let us consider the consequences which inevitably follow this apparently simple statement.

If we look at the biochemical machinery of a living cell in a purely pysico-chemical way, we have to admit that the efficacy of energy transfer coupled with the minimality of this transfer impose extremely rigid spatio-temporal constraints upon our idea about the nature of the events which take place within this cell. The amounts of energy transferred are not continuous but "quantized." The margin of spatio-temporal imprecisions is extremely restricted. If the amount of energy is not delivered in the proper place and if it is not released at the right time, it may be sub-minimal, so that the "expected" reaction would not take place, and the freed energy would not only dissipate in the surroundings but would also endanger the neighboring structures or processes. In this way a sort of close although dynamic (non-structural) relationship has to be recognized between the donor, or delivering, molecular system, and the acceptor, or absorbing, molecular system. They have to fit together. Otherwise, the energy transfer would fail completely, or be excessive, as in the example of the safe and the explosives.

We started our analysis of the nature of functional events with the example of the spermatozoon's movements. These movements are physically determined by the transfer of energy between the mitochondria localized in the spermatozoon's mid-piece, and the spermatozoon's tail, which propels the germ cell across the fluid medium. The energy of the tail movements is partially converted into the momentum of the spermatozoon's body and partially dispersed in the water. So this process does not seem to fulfill the criteria of efficacy and minimality. The movements of the tails are physically determined by the release of the chemical energy stored in the ATP molecule. This dynamic event may be considered as functional on the condition that the energy released by ATP is effective and not wasted. Similarly, the processes which lead to the production of ATP from ADP and the inorganic phosphate group may be considered as functional under the same conditions.

The constant production of high-energy bonds within the sperm mitochondria and their subsequent breakage might produce a great number of effects in the spermatozoon's structure. The energy liberated by hydrolysis

of ATP molecules might split many chemical compounds, might produce overheating of the sperm, might disperse in the surroundings. But no such effect is observable. The only effect, or dynamic process, which remains quantitatively proportionate to the hydrolysis of the ATP is the movement of the tail. And so we have to admit that if everything in the sperm is following the ordinary laws of physics, the whole, or almost whole energy output of the mitochondria located around the mid-piece of the.spermatozoon is being converted into the mechanical work of the tail. But let us imagine another, physically, or even physiologically, possible situation in which the ATP produced by the mitochondria is not used exclusively to move the tail but is dispersing its energy in the surroundings as well, so that the quantity converted into mechanical work decreased considerably. In this case, the movements of the tail would remain as determined by the ATP as they were before. Yet the hydrolysis of the ATP would,not be called functional, although the ATP was producing its normal, in the physical sense, effect upon the flagellum. The ATP would now remind us of the wind which is blowing and moving everything with a structure that allows it to yield under the impact of the energy flow. A restricted, selective energy flow characterizes functional efficacy. But it is not enough. The directly observable permanence of the spermatozoon's structure turns our attention to another condition or property which characterizes "functional" events.

The chemical structure of the spermatozoon is extremely fragile, and this structural fragility provides the best test of the minimality of energy transfer between the ATP molecule and the spermatozoon's tail. If the energy released by ATP molecule were supra-minimal, it would overheat the delicate chemical structures which are so crucial in restricting the energy transfer. The precision of the whole process would'diminish considerably, and, consequently, the whole process would not only stop altogether, but the release of energy in the wrong spatiotemporal coordinates might lead to irreversible destruction of the whole structure.

Generalizing these observations we may say that the nature of the processes which take place in the living organism is such that it would necessarily endanger the whole structure if the process were not functional, i.e., if the energy were liberated in a locally and temporally random, non-restricted way.

Now if the functional efficacy is minimal with respect to a given concrete effect or change, no further decrease of the energy used is possible. If the energy is lowered the effect is not produced.

In the case of functional processes, the energy seems therefore to be restricted, channeled and minimal. The restrictions are imposed by the form (structure) and that is the reason why in all the functional processes there is a close dependence between the form and the effect. In the case of tides, storms, volcanoes and other physical dynamic processes, even if a channelling, a restriction of the energy, is observable, the effects are divisible parallel to the division, or decrease, of the energy flow, which in these cases is never minimal. In a wristwatch, on the other hand, the energy flow is almost minimal, so that a relatively small increase in the friction of the parts stops the process completely.

The idea of a purely physical efficacy based on the energy flow which is minimal to the effect, coupled with the idea that the minimal structure determines this minimal flow of energy and secures the efficacy of the whole process, constitute a set of criteria which are verifiable by observation of the process itself. This idea does not postulate any necessary link between the effect observed and the given concrete set of causal, physically determining, influences, for the same effect may possibly be produced in many different ways. Yet if a given concrete set of influencing agents, the causal agency, however complex it may happen to be, and the effect produced, are compared, the judgment about the amount of "wasted" energy and redundant structural components of the agent is based not on any third, external element, but on a simple comparison between the characteristics of the influencing changes and the characteristics of the provoked change.

This idea has been already stated by several authors, but they usually tied it with the idea of purposiveness, so that the purely physical nature of functionality was in a sense obscured by the consequences of metaphysical difficulties involved in the whole conceptual framework of teleol-ogical considerations.

Mace, writing about some characteristics of the teleological processes, expresses himself in -this way:

> "A teleological sequence is a more or less economical arrangement of causes in a manner which secures the realization of an end..." (1935/37).

> "causal sequence has a teleological character whenever a sequence of events occurs which satisfies certain conditions —[and the third condition is stated in the following manner]...with repetition the process approximates to a form in which every phase is relevant to the production of the...[effect]..." (1935/45; see also Sommerhoff, 1950/ 52, 54, 60).[79]

The notion of the "end" ceases to be externally determined, once the process itself happens to be minimally effective to its only effect. In the seme sense there remains no reason to attribute any external "purpose" to this effect.[80] Of course, it may happen, and, in fact, frequently does happen, that several functional processes are linked together in a sort of causal chain. But if such a chain is discovered and observed it can be reduced to the sum of several elementary functional influences.

4.9 The nature of the functional event

In the light of the previous analyses and rudimentary insights, the nature of a functional event may be defined in the following way:

a) A functional event is a. special case of a physical event called influence. It implies a dynamic relation between at least two separate physical entities. "Separated" means that each one of those entities may exist, persist, despite the absence or destruction of the other.

b) During the functional event, one of those bodies is influencing the other, while the other is influenced by the first. "Influencing" or "being influenced" means that each of the two bodies involved in the functional event has an intrinsic capacity to exist in at least two different states which are temporally exclusive -- i.e., while the body is in one of them, it is physically impossible for it to exist in the second. The dynamic

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[79] We can also find a similar idea in Rashevsky's "principle of adequate design," which is that "all properties of biological systems are so devised as to serve optimally, or at least adequately, a preassigned functional performance. A proof or disproof of the principle is possible only after a proper definition of the attributed performance" (Rossler, 1972/205). Of course, our claim is that the proper definition of functional performance refers to the maximally restricted physical efficacy of a process. This removes the subjective element from Rashevsky's idea of "adequate design" and reduces the teleological meaning of the term "preassigned" to the concept of developmental, epigenetic observational events.

[80] Nagel writes: "When a biologist ascribes a function to the kidney, ... he ignores as irrelevant … any other systems of which it may also be a constituent. … A physicist … is reluctant to ascribe a 'function' to the sun's radiation, because no one part of physical system of which the sun is a part is of greater interest for him than is any other such system..." (1961/ 405). If, however, the nature of "functionality" is defined in terms of a sole, single, minimal effect, then a correct usage of this term does not signify an arbitrary mental "interest," but refers to the restricted efficacy of a causal event.

relation of the physical influence is *non-symmetric,* although its characteristics are describable in terms of the empirical laws of physics and chemistry. For instance, burning wood can cause (influence) water to boil, but not vice versa, or the movements of the moon pull (influence) the water in the Earth's oceans, and not vice versa (See Bunge, 71/129).[81]

c) In the case of a functional event, the change produced in the influenced body is intrinsically irreversible. Intrinsic "irreversibility"means here that the return of the changed, "influenced" body to its original state, although physically possible, cannot be attributed to the intrinsic capacities of this body. It means that states of dynamic equilibrium, such as the movements of a pendulum, the movements of the moon round the earth, the bouncing of a rubber ball provoked by a throw, and so on, although they all imply inevitable positive change in the amount of the entropy of the system, or entity, are not examples of the sort of change of which we are speaking in the context of a functional event.[82]

d) The "atomic" functional event is characterized by the fact that the change in influencing body is minimal with respect to the intrinsically irreversible change of the influenced body. "Minimal"means here that

(1) a certain intrinsically irreversible change is produced in the influenced body;

(2) the amount of energy needed for the production of this change is determined by the intrinsic nature of the change, and is expressed in terms of physical laws;

(3) a necessary (in the given-physical environmental conditions) raise in the entropy of the system (AS) is taken into account (see, e.g., Morowitz, 1970; Marsden, 1973), and

(4) the change of the influencing body has

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[81] "Mechanisms—are cause-and-effect relationships that determine the occurrence of certain events" (Saunders, 1970/108). Functional event represents quite obviously a mechanistic idea.

[82] Nagel writes: "It is an open question...[whether] the physical systems such as pendulum at rest',.. .really do conform to the definition of 'directively organized' systems..." (1961/419). If'our analysis of the functional event is correct, neither a pendulum at rest nor the same pendulum in movement represents a case of a "directively organized" system, for it might be that it was "created" by pure chance. Only a repetitively appearing functional event may raise a justified search for its origin and this origin may happen to be "directively organized."

produced only this sufficient and minimal amount of energy.

(e) We may add as a sort of logical corollary that the functional event operates in an "all-or-none" way.[83] The irreversible change in the influenced body produced by the sufficient but minimal influence is necessarily discontinuous.

How then may we explain that some physiological dynamic events do show a practically continuous gradation, on the macroscopic level of observation? The amount of glandular excretion, for instance, or the intensity of a muscular contraction, may be regulated in an apparently continuous way. The correct explanation of this fact has to start with the distinction between the biochemical level of a given process and its macroscopic, overall manifestation. In a "single" gland, or in a "single" muscle, hundreds and thousands of identical "atomic" functional events take place simultaneously, in a "parallel" way. This explains why the overall effect reaches the macroscopic level of observability, and why the discontinuity of the process (all-or-none effect) is seldom observable.

We may say that the *"functionality"* of such macroscopic dynamisms as kidney activity, liver activity, brain activity and so on, has to be conceived in an analogous sense, which derives its proper meaning from the idea of the "atomic" functional event, which is always describable in terms of molecular, or chemical, reaction.[84]

Functionality is a phenomenon which appears primarily upon the lowest level of cellular organization. A chemical change, a chemical influence, may be functional or not. A chemical synthesis, or lysis, may be functional or not. For instance, the lysis of the ATP may be functional in

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[83] "Bowditch (1871) discovered that the heart muscle, under whatever stimulus, will contract to the fullest extent or not at all. In the heart, stimulation of any single atrial or ventricular muscle fiber causes the action potential to travel over the entire atrial or ventricular mass, or not to travel at all. In other muscles and in nerves, this principle is limited to individual fibers; i.e.., stimulation of a fiber causes an action potential to travel over the entire fiber, or not to travel at all. Called also all-or-none law" (Dorland's, 1974/60).

[84] On this point our opinion is contrary to that of von Bertalanffy. He believes that life phenomena "...are esentially non.-additive and therefore cannot adequately be dealt with by analytical methods. You cannot split them into isolable elements and causal trains..." (1972/19). This judgment seems to be exaggerated. Not only mental analytical'methods but even physical ones are applicable, and even necessary, during the investigation of life phenomena. But von Bertalanffy may be quite right if his statement is to be understood in the sense that the results of an analytical process have to be reconstructed into a faithful redescription of the original whole.

one concrete situation and not-functional in another. We see that the concept of function implies physical or physicochemical concepts, but restricts them according to the broader context. The amount of free energy liberated during the hydrolysis of ATP depends on many physical factors (see, e.g., Yost, 1972/230), and it may happen that a change in the immediate surroundings may so affect the hydrolytic process that the amount of free energy liberated will fall below the level of efficacy. The energy transfer will be non-effective.

4.10 Functional causal chains and the triggering event

In our example of the spermatozoon's tail we have seen that the causal process inaugurated in the mitochondria ended in the fluid medium in which our spermatozoon was moving. The energy provided by the complex chemical processes going on in the mitochondria was finally dispersed among the water molecules, increasing their thermal agitations. For this reason we have said that, in our example, the final physical event was not-functional. Between the events observed in the mitochondria and this final non-functinal event provoked by the movements of the tail, a number of functional stages might be recognized. The hydrolysis of the ATP molecule which functionally affects the tail was arbitrarily selected from a long and only framentarily known sequence of functional events which determine the spermatozoon's loco-motory movements. We know how this functional causal chain ends. But how does it start?

The problem of the release of functional events does not enter directly into the sphere of our considerations. Yet it may be useful to mention the so-called "triggering" environmental effects commonly observed in living organisms. The neural excitation of a muscle fiber may serve as a good example of a triggering event. An electrical, or neurohormonal "stimulus" which releases the functional transfer of energy taking place during locomotory movements does not convey the energy of muscle contractions. From the point of view of energy transfer, the "triggering" event is usually so small that it cannot explain the physical nature of muscle contraction,, whether that is functional or not. It only throws the "energy-loaded" first step of functional chain out of its original equilibrium state. To illustrate

this better we may imagine that a watch has been wound up, but that its balance wheel has remained in some position such that the watch did not start. Usually the random movements of our hands throw the balance wheel out of its equilibrium position, and the watch then starts.

A triggering event may originate in the organism's enviroment or within the organism's own sphere. Some biological processes are triggered by changes in the environmental parameters, some others by specific "immanent" signals, by hormones, for instance.

Some environmental influences, however, consist in a true transfer of energy into the living body. This is the case in the photo-synthetic process. The intensity of light energy which "falls" on an organism is too small to be effective, for otherwise the organism would be quickly and irreparably damaged. A special structure of photosynthetic units reorganizes the random quantized energy of photons, channelling them into specific points and times, so that the stream of solar energy becomes just effective, i.e., functional (see Mahler § Cordes, 1971/558ff.; Yost, 1972/308-312; Park, 1971/25-40). The photosynthetic process constitutes the ultimate, or rather primary, source of energy for all other dynamic processes of life.

After this complementary digression we will turn back to the analysis of our functional event.

4.11 The concept of "atomic" functional event — heterogeneity and integration

The idea of intrinsic *integration* of functional event may be better understood if we consider the *simplest* possible case of this event. We may call it the "atomic"functional event.

Any "atomic" functional event may be schematically represented in the manner shown in Fig. 4.1. From this scheme we may realize that the concept of functional event implies a physical interaction between at least two different entities, or groups of entities. The "triggering event" does not seem to be necessary if the change A-a occurs spontaneously. The concept of functionality does imply, however, an environmental system of entities or even processes, and the properties of this environmental system determine the physico-chemical possibility of any interaction between the entities Alpha and Beta, and the value of ΔS (raise in the entropy of the system). The concept of functionality implies the validity of the basic physical laws, such as the principle of the conservation of energy, the thermodynamical laws, and the like. But it does not presuppose any specific *causal* order. It

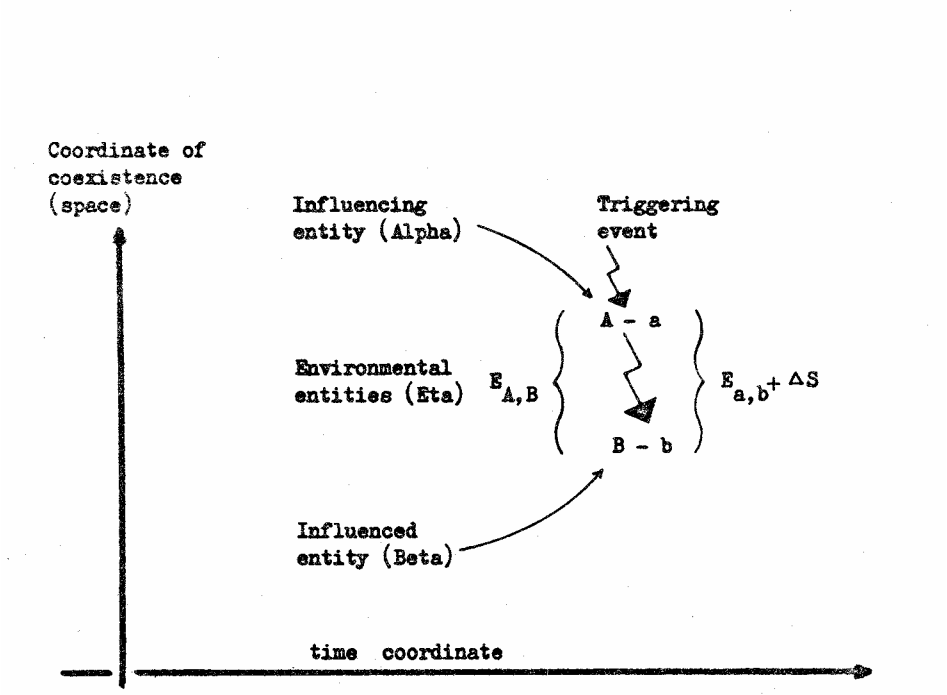

Fig. 4.1 Functional event. The value of ΔS is minimal for $E_{A,B}$

is quite possible that a single "atomic" functional event will occur as a result of independent, purely random physical interactions. Still, this heterogeneity, both structural and dynamic, is irreducible. The states A and B are irreducible, one to another. The environmental entities and processes are irreducible to the interacting entities. What is more, we cannot change any of the above-mentioned elements without changing all the rest of them. If we do, the process will cease to be functional. The reason for this condition flows from the fact that any change in a concrete overall pattern of the system will affect the value of ΔS, or even the efficacy of the influence occurring between Alpha and Beta. In the light of these considerations we may understand better the fact of the "machine-like" activity- of some biochemical processes:

> "Certain molecules are invariably present and serve in the same capacities in the cells of all living organisms. ATP is almost always the molecular instrument for energy conservation and storage. D-Glucose is almost always the particular sugar that serves as one of the fuels in the reactions leading to the release of

> utilizable energy...Since the molecules are designed for the machines, and the machines for the molecules, the area of permissible variation was reduced to negligible proportions. D-Glucose could not have been replaced by any other sugar without necessitating major .changes in the large numbers of interlocking parts that constitute the machine concerned with the glycolysis of D-glucose. The inviolability of...[these]... molecules is a consequence of this multifaceted fitting together of parts in highly complex machines. One cannot easily change from AC to DC current when all the equipment has been constructed for 110 volts. [But] the analogy is a loose one, its validity resting on the assumption that the changeover is not only difficult but impossible...Once the 'definitive' forms of the basic systems of the cell were achieved, the molecular pattern of these systems became fixed; thus, the molecules that participate in these systems have become the invariant features of all cells" (Green and Goldberger, 1967/27-8).

Therefore, we might say that every concrete form of functional event has its own specific, intrinsic, heterogeneous, four-dimensional pattern.[85] This pattern is *indivisible,* in the sense in which the atomic functional event is "quantic," i.e., it is additive but not divisible.[86]

We may take any textbook of chemistry or biochemistry, select any chemical reaction which consists in the transfer of energy between molecules, and we may estimate a minimal set of structures, the interacting elements and the entities present in their environment, and the precise spatio-temporal pattern which will provide the purely physical conditions for the "functionality" of this reaction, where "functionality" means *effectivity* accompanied by a minimal loss of free energy of the "system." Then we will realize that the minimal set of entities involved and their spatial pattern is *intrinsically* and *irreducibly heterogeneous.* At the same time, being minimal, it is indivisible with respect to the efficacy of the process in question.

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[85] It seems that the technical difficulties encountered by early biochemists in obtaining "pure," i.e., homogeneous, substances from intrinsically heterogeneous and dimensionally molecular functional units may explain the gap between the statistical approach to basic biochemical reactions and the actual, non-statistical nature of these reactions (see Fruton, 1972/18-20).

[86] "There is a growing realization that all biochemical functions within the cell are integrated spatially into a tightly organized hierarchy of ever larger functional units. Interaction of molecules within the structural framework is highly restricted and at the same time favored in harmony with the over-all purpose. In this respect, the coordination of biochemical reaction programs is more akin to the meshing of gears in an intricate mechanical clockwork than to any notions derived from the study of enzymatic reactions in aqueous solution..." (Noll, 1965/105; see also Commoner, 1961; Oparin, 1964/40; Luft, 1971/3).

If, then, a given, concrete chemical reaction is repetitively observed, and at the same time it fulfills the criterion of functionality, we must admit, because of purely physico-chemical reasons, that the "uhole" set of structural conditions is repetitively fulfilled.

We may conclude that functionality of an event implies the integrity of a heterogeneous spatial pattern, and that the repetitivity of the same functional event implies the repetitive appearance of a specific heterogeneous spatial pattern.[87]

4.12 The notion of "functional structure"

From the previous analyses it should be quite obvious why the structural element is so crucial in the case of functional events. Any functional event is decomposable into "atomic" functional events. The "atomic" functional events consists of a transition between two states, essentially describable in terms of static structures. In the first state we have to do with an energy-loaded influencing agent Alpha and with another entity Beta which is ready to absorb the energy.

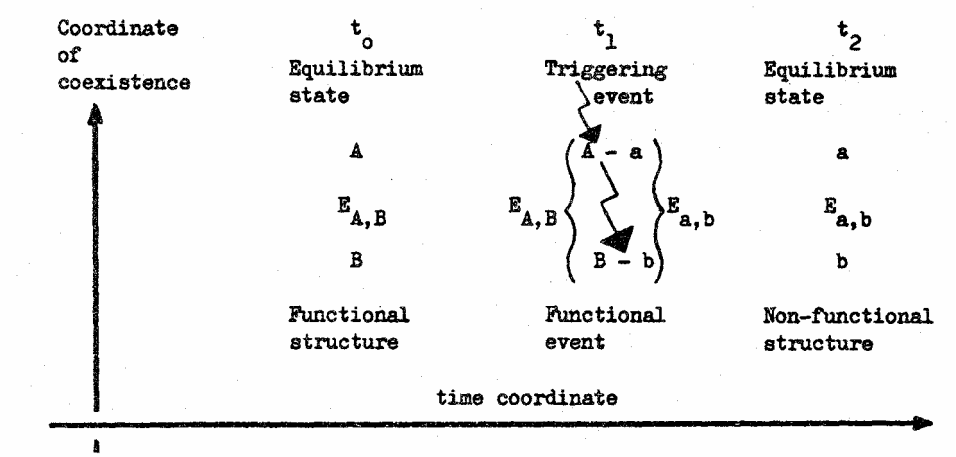

Fig. 4.2 functional structure and functional dynamics. Functional event constitutes a four-dimensional phenomenon. It implies an irreversible change of at least two entities which is determined by the transfer of energy between them.

[87] Nagel asks: "… what spatial structures are required for the exercise of specified functions, and whether a change in the pattern of activities of an organism or of its parts is associated with any change in the distribution and spatial organization of the constituents of that system. That is obviously a matter [he adds] to be settled by detailed empirical inquiry..." (1961/426). The problem of the origin of the "spatial structures required for the exercise of specialized functions" cannot, however, be resolved by a simple redescription of these structures.

This state, which we may call "functional structure," will remain in a rather rigid spatial relationship, "expecting" the triggering event which will release the energy from the influencing entity. Once the energy is released, the entities Alpha and Beta enter a new static phase. It may happen, of course, that the entity Beta, passing from state B to state b, has transferred the received energy into a third entity Gamma, and transformed it from c into C. It may be that this transfer of energy is functional, too. In this case we would have to deal with a chain of functional events composed of two "atomic" events. But in any case, the structures a, b, will remain in the non-functional state unless they are transformed back again into states A and B, respectively. Spontaneous reversal, however, is excluded, according to the notion of "influence" and "intrinsic irreversibility" which enters into the description of the functional event.[88]

4.13 On some consequences of the concept of functional integration of structures

In order to shorten our considerations, we will take for granted the rather obvious fact that the chemical entities, or molecules, involved in the process of energy transfer within the simplest living bodies are structurally extremely complex and that they are not present in the mineral world. Bearing this in mind, let us analyze the conditions for repetitivity of an "atomic" functional event. As a result of this event an influencing molecule (or set of molecules) Alpha passes irreversibly from the state A into state a, and the energy-absorbing molecule (or set of molecules) Beta passes irreversibly from the state B into the state b.

Once the above reaction has taken place, we are left with the a, b and the environmental entities Eta which, for the sake of simplicity, may be considered as unchanged. These structures, as we have seen (see Fig. 4.2) are non-functional. Before the *same* functional event can be repeated, we have either to provide new molecules Alpha and Beta in the states A and B, or the molecules a and b which have remained from the first reaction have to be transformed from the state a and b back into states A and B, respectively.

[88] On this point, although we fully accept Sonneborn's generalization that "function is intimately connected with molecular structures," we cannot share his conviction that: "Preexisting structure determines processes that lead to different structures and different processes in sequences that are self-determined at every step and that lead cyclically to the starting point" (1965/217) . "Self-determined" cyclical return to the starting point seems to be a sort of paraphrase on the molecular level of the ancient and discredited idea of "perpetuum mobile."

The first alternative, which we may call "epigenetic," means that a rather complex organic molecule, since we are talking about biochemical phenomena, has to be produced from inorganic matter. The repetitivity of the same functional event will necessarily postulate the repetitive *"de novo"* appearance of heterogeneity from the relative homogeneity of the mineral salts, water and atmospheric gases present in the surroundings. At the same time, the "useless" entities Alpha (a) and Beta (b) will have to be eliminated from the functioning system, for their presence would affect the spatio-temporal pattern of this system, and consequently its functionality.

The second alternative, which we may call "energy storage" alternative, would mean that a special system has stored enough of Alpha entities in the state A to secure the repetitivity of our functional system. This alternative implies the explanation of the origin of:

a) a system producing Alpha (A) entities;

b) a system capable of storing them;

c) a system dispensing them gradually.

It does not seem that the "energy storage" alternative is very much simpler than the first, i.e., "epigenetic" alternative. In fact, it postulates a more complex epigenetic process capable of producing both the storage system and the dispensing system. In either case, then, we are forced to accept the epigenetic process as the only rationally adequate explanation of the repetitivity of functional events.

Repetitive functional events, such as the production of action potentials in nerve fibers, the repetitive beats of the heart, or the repetitive movements of cilia and so on, take place continuously in living organisms.

They reveal the "all-or-nothing" property, they are obviously and necessarily connected with the transfer of energy, they repetitively appear in practically isothermic conditions, and the structures involved are apparently stable.[89] All this strongly suggests that our abstract concept of "atomic" functional event represents a non-arbitrary notion of the essential properties of these events.

[89] "While energy input is needed to create and maintain non-random diversity, the difference between just any non-random state on the one hand and the repetitive and conservative order of diversity in organisms on the other, is not spelled by the scalar values of energy, but by the vectors of its channeling; just as it is the ordered channeling that makes a given amount of energy fed into a machine yield useful work, instead of dissipating itself in an explosion." (Weiss, P., 1961/67-8).

But the *repetitivity* of these events does not allow us to accept the hypothesis about the *random* origin of the conditions which are physically necessary for the appearance of these events.[90] We have discussed two non-random, hypothetical, explanatory models: The "epigenetic" model and the "energy storage" model. The former turns out to be reducible to the epigenetic events discussed in the previous chapter. The latter postulates an even more complex epigenetic process.

Therefore, it seems that a non-random epigenetic process constitutes a sort of inevitable reality which has to be admitted whenever a repetitive functional event is observed. And this has led us back to the notion of the developmental path, and ultimately to the notion of the "life cycle." We may repeat now the questions we posed at the beginning of this chapter.

We asked whether the so-called *functional* event represents a distinct, objective category of dynamic events. The answer is in the affirmative, but the intrinsic nature of this event seems to be purely physico-chemical. Yet the event as such postulates a specific integrated heterogeneous spatial pattern. The observed repetitivity of functional events cannot be explained in terms of random physical events. It seems plausible that the basic epigenetic phenomena, discussed in the previous chapter, provide a satisfactory answer for this repetitivity.

The second question we formulated was whether the concept of the functional event has some consequences on the notion of integration of the epigenetic phenomena of the "life cycle." Let us now discuss this problem in some detail.

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[90] The repetitivity, in fact, constituted one of the most important hints which have made the discovery of the nature of some biochemical mechanisms possible. Describing striking diversity of the cellular ultra-structures, Porter states: "Beside from being constant for any single type of cell, these patterns are found to repeat to some degree in cells performing similar functions. It was in fact this tendency, brought to light by comparative cytology, which gave the first clues to the functional properties of these structures" (1963/145).

CHAPTER FIVE

PHENOMENA. OF LIFE -- DEVELOPMENT

5.1 The problem of the origin of functional structures

In the previous chapter we have analyzed the dynamic relationships between the coexistent structural elements of the phenotype. As a result of this analysis we were able to recognize a special form of relationship which seems to characterize those dynamic phenomena of life commonly referred to as "functional." Locomotory movements of the spermatozoon and the effects of ATP hydrolysis constituted the concrete empirical, observational background of our considerations. The results of our analysis were then generalized on the basis of premises such as the efficacy, isothermy and structural integrity of energy transfer processes in the body.

The notion of function, on the molecular, supra-molecular and cellular levels, was defined in the purely physico-chemical terms of the "just efficacious" transfer of energy between two separate structural elements. The purely physico-chemical conditions of such a transfer have led us to the notion of intrinsic indivisibility, or minimality, of a complex, heterogeneous functional system. We have defined the exact meaning of the term "functional structure." The irreversibility of changes produced during the functional transfer of energy has helped us to realize that the return of a functional system to its functional structure, or state, cannot be explained in terms of the intrinsic properties of the system.[91] We have concluded, therefore, that the directly observed repetitivity of a func-

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[91] It is important to realize the intrinsic irreducibility of the functional and developmental events. The error of earlier "mechanistic" trends in biology did not consist in a claim that some of the bodily dynamisms can be adequately explained in terms of molecular machines, but in the claim that all dynamism of life is "mechanistic" Florkin rightly states: "...the study [of the cell]...is exposed to the same pitfalls as those the first physiologists met when the whole organism imposed itself on their sensorial perception in the form of *anatomia animata.* The frequent use, in recent times, with reference to cells,-of such phrases as 'biological machines,' or of 'molecular technology' indicates that the pipes, sieves and levers of the iatrophysicist's and his naive biophysics are already around the corner, ready to take their place in a new 'cell biology'...and to postpone the development of a more abstract scientific treatment of the cellular polyphas-ic system of integrated macromolecules..." (1972/316). On the irreducibility of functional to developmental processes see also Oppenheimer (1969/215) and P. Weiss (1961/47).

tional event has to be explained in a way which will provide an answer to the question of how the functional structure originates.[92] An analysis of the observational aspect of this origin will constitute the next step in our discussion of "question-raising" phenomena of heredity.

The crucial point of our problem is reducible to the *intrinsic* heterogeneity of the functional event. Not only two interacting molecules, or molecular systems, have to be different and proportionately complex, but the environmental conditions must also be specific and complex. If we conceive the *separate* but *coexistent* entities involved in an atomic functional event as separate hereditary traits, and consequently as the final stages of two different developmental paths, the *necessary* integrity of the elements involved in the functional event, together with the repetitivity of this event, will postulate a *non-random* interdependence between the whole set of the developmental paths.

If, then, the entitative structure of the functional event constitutes a sort of indivisible "whole," then the whole set of developmental paths which leads to the repetitive appearance of functional structures should also be conceived as a sort of indivisible "whole". On the basis of the above discussion we may construct criteria for the distinction between *a developmental* and a *non-developmental* epigenetic event. In fact, the concept of epigenesis as such is not necessarily related to the concept of functional relationship. We may easily imagine epigenetic events which lead to non-functional systems. In pathology, examples of epigenesis which lead to non-functional structures are commonplace.

Before we attempt to define more precisely the criteria which distinguish the developmental events from the other epigenetic but non-developmental ones, let us examine some concrete examples of developmental processes. This will help us to abstract the essential element distinguishing this form of epigenetic events.

At the first step of our considerations we will discuss some observational details of spermatogenesis and some details of the anabolic bio-

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[92] The authors of such outstanding treatises on the phenomena of development as Saunders (1970) and Berill (1970, 1971) confess the virtual lack of an adequate theoretical conceptual framework in this domain. Saunders, for instance, writes: "the continued adduction of data about developmental processes will add disproportionately little to an understanding of them." Berill confesses: "The development and organisation of cells to form multicellular organisms, in spite of a monumental mass of observations is a field in which understanding is minimal" (1970/842; see also Baer et al., 1971/2).

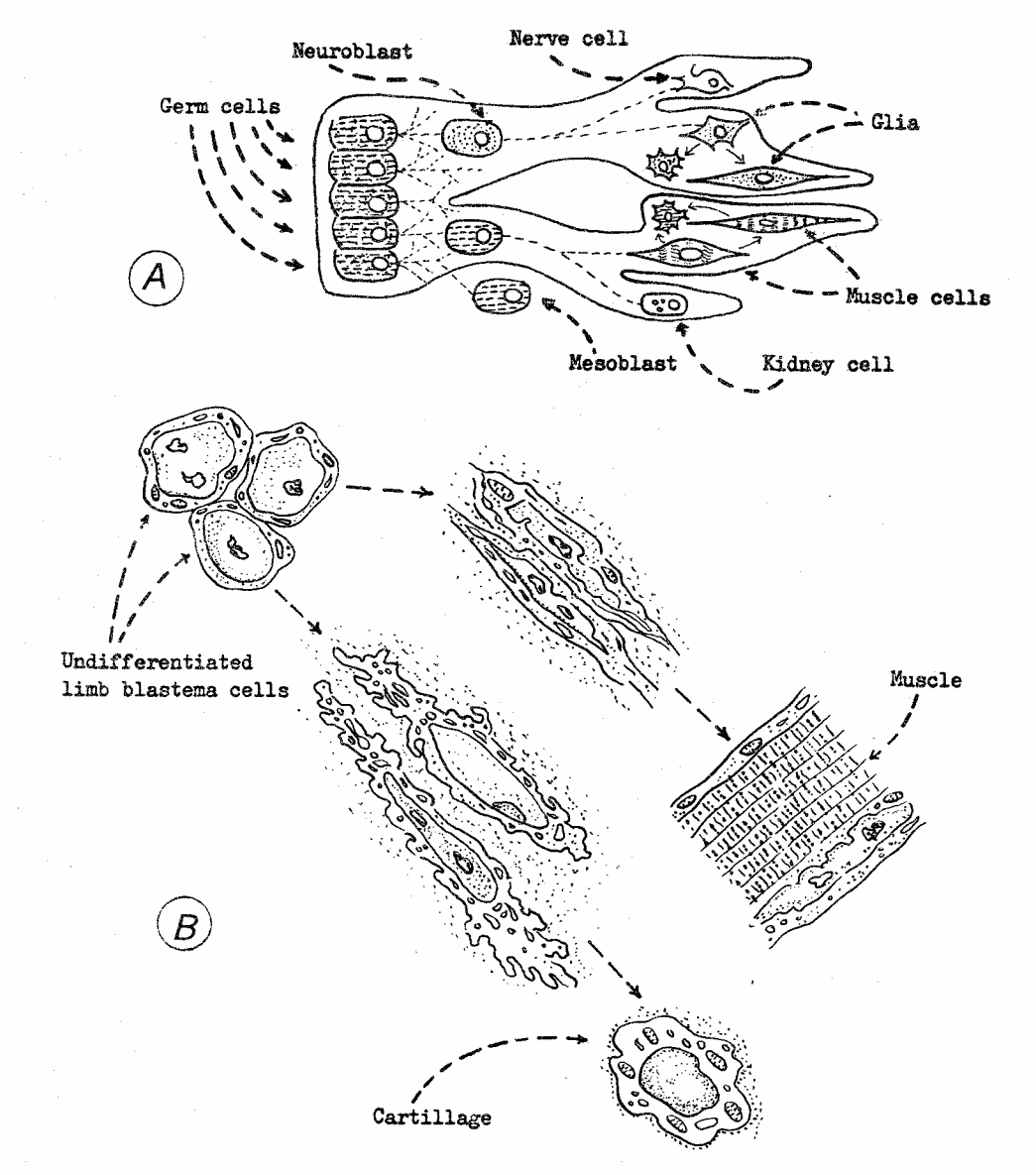


Fig. 5.1 Differentiation process in metazoa.(After Berrill,1971, Figs. 21.7 and 21.9)

A - Phenotypically identical germ cells undergo the transformation into a variety of functionally specialized cells.

B - Main steps in the transformation of phenotypioally identical mesenchyme cells into cartilage cells and muscle cells.

chemical pathway which produces molecules of ATP. Using the previously defined concept of "functional event," we will try to grasp the most essential characteristics of both spermatogenesis and "ATP-genesis." Then we will try to generalize the inevitable logical consequences of our investigation in the form of criteria distinguishing between the epigenetic event which leads to a functional structure and the epigenetic event which does not. These criteria will constitute the definition of the developmental event. Finally we will discuss the problem of the repetitive appearance of developmental events. This will help us to understand more clearly the nature of the "life cycle," and at the same time to formulate more precisely the conditions which have to be fulfilled by an adequate concept of genotypic agency.

5.2 On the concept of differentiation and on some theoretical complications involved in it

The term "differentiation" is commonly used with reference "to those phenotypic phenomena which start with a number of observationally identical cells, or subcellular components (plastids), and end with a number of structurally and dynamically different cells or subcellular components.[93] The term, in fact, is a synonym of "epigenetic process," though it is restricted to the microscopic or ultra-microscopic observational scale range.

The concept of differentiation in unicellular organisms has the same meaning as the concept of the "life cycle." In multicellular ones the differentiation of a cell leads to its final, functional (see Fig. 5.1), adult stage, which is not proliferative and in normal conditions (with the sole exception of gametes) does not start a new "life cycle" (see Saunders, 1970/109).

In spite of the fact that the phenomena of intracellular structure and dynamics are directly observable under the electron microscope, the idea of differentiation is far from being clear. The complexity of the registered phenomena, the complexity of the larger context in which they are observed and an awareness of the need for an adequate theoretical explanation provoke quite often a specific mental attitude which in a single idea lumps together observational data and the explanatory speculations.

[93] "Inherent in the concept of differentiation is the notion that one kind of cell is transformed into another kind, different in structure, function and chemical composition" (Kenyan, 1973/86).

This lack of clarity may sometimes give rise to a doubt as to whether in the case of differentiation, we have to do with evidence for the existence of a truly epigenetic phenomenon.

There are basically two main currents of interpretation which debilitate the meaning of the direct observational evidence for the reality of the truly epigenetic nature of differentiation phenomena.

The first current of thought introduces the distinction between the process of "self-reproduction" and the process of "true" differentiation. If, for instance, a cell divides into two cells, if a chromosome replicates, if a number of mitochondria arise by the multiplication of a single mitochondrion, some authors are prone to deny that we have to do with a truly epigenetic process (see, e.g., Bonner, 73/1, Holtzer, 70/77). Let us forget for a while the tremendous complexity of chromosomal, mitochondrial or cellular structures. Instead, let us consider something simpler, like a water molecule. It is quite obvious that even such a simple chemical compound cannot split into two identical entities.

In the physical world we do not have any example of true "self-replication." If on the other hand we have to do with complex structures such as chromosomes, mithochondria or cells, we have to admit that two supposedly £nd observationally) identical cells contain a double set of structural components, one of which must have been built *"de novo"* from inorganic matter. The presence of the other, parent organism, or organelle, may constitute an observationally, empirically necessary premise of this *"de novo"* construction, but this fact does not detract anything from the reality of the epigenetic origin of the next copy. The process of "self-replication" is essentially different from the process of crystallization. During the latter process, the already formed entities come together and a new level of structural hierarchy appears. Crystals are not "self-replicating" but "self-aggregating."

Writing about the cell cycle Mitchison states:

> "There can be little argument about the presence of morphogenesis and differentiation during mitosis. The cell undergoes profound changes of structure with the condensation of chromosomes, the disappearance of the nucleolus and the nuclear membrane, the formation of the mitotic apparatus and the separation first of the

> chromosomes and then of the daughter cells. The only difference between this type of differentiation and that of a multi-cellular organ or organism is that the latter involves many cells and there is almost certainly some cell-to-cell communication, whereas the former happens within the confines of a single cell" (1973/2).

The other speculative idea which tends to reduce the reality of the epigenetic nature of cell differentiation, or organelle differentiation, introduces prematurely "question-solving" ideas into the report about directly observable phenomena. So, for instance, Schjeide and DeVellis (1970/ 6); Waddington (1966/15) stress that the differentiation is based upon a preexisting state.

It is obvious that nobody can explain away the fact of the *continuity* of life phenomena. In this sense there is no single case in which we might be allowed to deny that a phenomenon of life is founded, in a way, upon a pre-existing state. But the question-raising element of life phenomena does not consist in the fact of the continuity but in the fact of repetitivity of epigenetic processes. The opinion we are discussing now, especially in the case of Waddington's statements, may bring to mind the preformationist's ideas. They are re-stated here in a more sophisticated form, but the essential element remains the same.

Still another form of this speculative framework has recourse to the notion of "cryptic" determination, which, although invisible, is nevertheless supposed to be real and which explains away the apparently epigenetic course of events. Holtzer et al, for instance, claim that an "un-dif-

ferentiated" cell does not exist at all. Even such complex, apparently developmental, epigenetic processes as myogenesis (gradual formation of muscle fibers), erythrogenesis (gradual formation of adult, functional erythrocytes) and chondrogenesis (gradual formation of cartilage tissues) are nothing else than a transformation of one form of complexity to another (1972/230).

As we remember, the notion of epigenesis (section 3.20) has no specific meaning if there is no real change from a less complex state to a more complex one. If we refuse to recognize the reality of epigenetic events on the level of phenotypic reality, the "question-raising" element of genetic theory will vanish altogether. The apparent epigenesis observable on higher ranges of the observational scale will be reduced to the non-epigenetic events observed upon its lower levels. The proper and ultimate explanation of the "life cycle" and its repetitivity will amount to its re-description in terms of molecular structures and dynamisms.

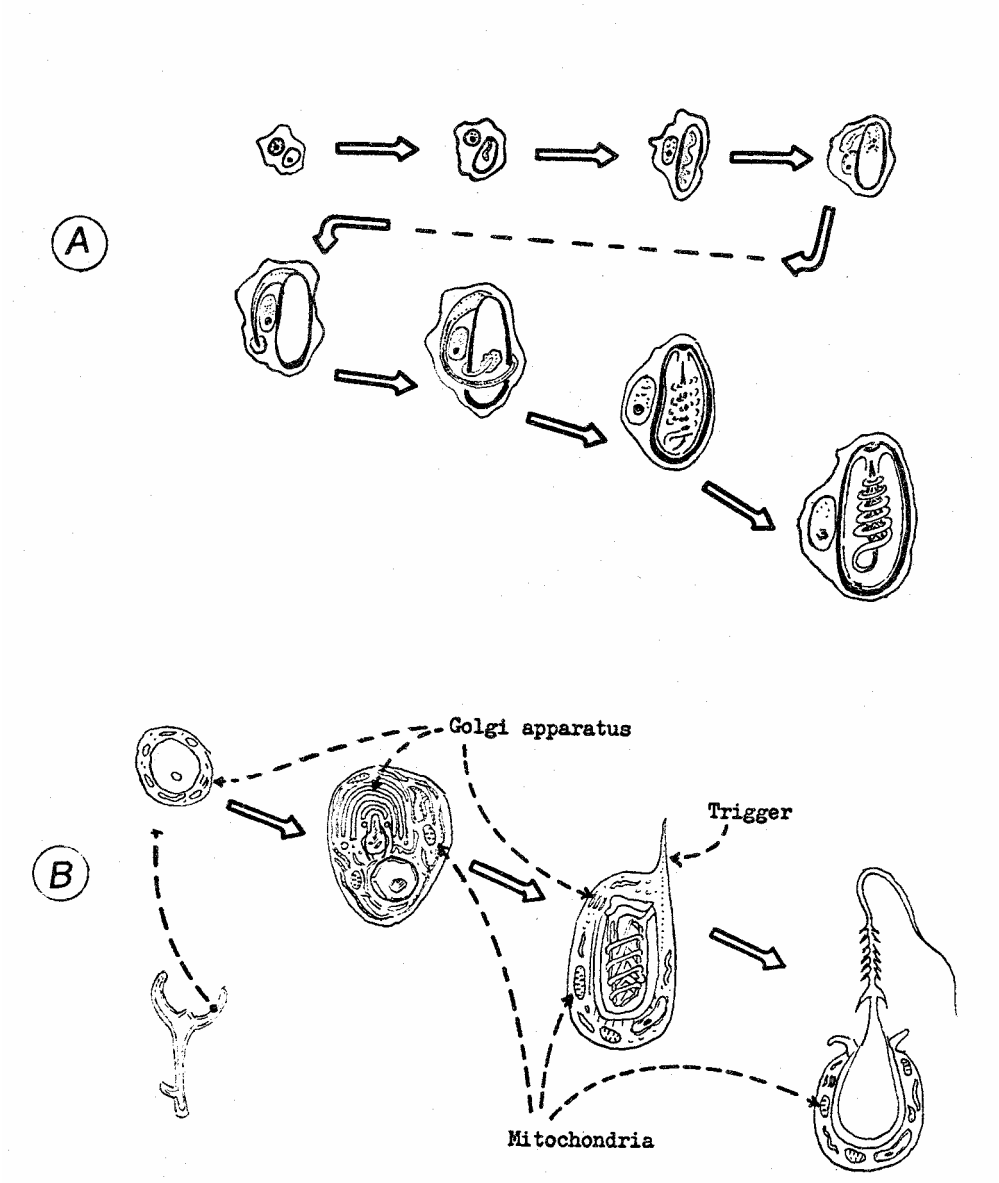


Fig. 5.2 Differentiation of nematocysts. A - Some stages of epigenetic,developmental transformation of cnidoblast into the functional structure of nematocyst (After Mergner.Natur Museum,94/1964/22). B - Hydra's organism, undifferentiated interstitial cell, cnidoblast. Kote fully developped Golgi apparatus and endoplasmic reticulum (EH), the mature nematocyst before and after the release of trigger.(After Novikoff & Holtzmann, 1970/212)

In this chapter we will not try to analyze the validity of this claim which, in a way, explains away, prematurely, to say the least, the distinction between the phenotype and the genotype. But in our

further discussion on the nature of the genotype's agency and the theory which identifies the genotype with the DNA molecule, we will return again to the preformationist opinions mentioned above and we will try to judge to what extent they were right in their claims.[94]

We may add that in an earlier period of studies of differentiation phenomena the priority of observational evidence has led some authors to the postulate of a true change in the hereditary material, or genotype (see, e.g., Puck 1957/14). This may serve as an illustration of another extreme opinion, opposite to the previously mentioned "preformationist" concept of Holtzer, Bonner and Waddington.

But the majority of authors describe the process of differentiation in its epigenetic form without trying to solve the "question-raising" element of this empirical evidence (see, e.g., Weiss, 61/42; Nossal, 1966/ 343; Burnett, 1968/109-10; Trinkaus, 68/1; Hildebrandt, 70/158; Haurovitz, 1969 /66; Donachie et al. 73/9; Garrod and Ashworth, 1973/407; Lerner and Dixon, 1973/ 85; Mitchison, 1973/209).

Nothinger (1973/18) and Gurdon and Woodland (1970/41) underline the necessity for a clear distinction between the phenomena of truly epigenetic differentiation and the concept of "determination," which belongs to the realm of genotypic categories.

5.3 Representations of the processes of differentiation

The differentiation process may be observed directly, but that does not mean it can be easily represented and communicated. In the case of this concept, far more than in that of functional events, photographs and drawings

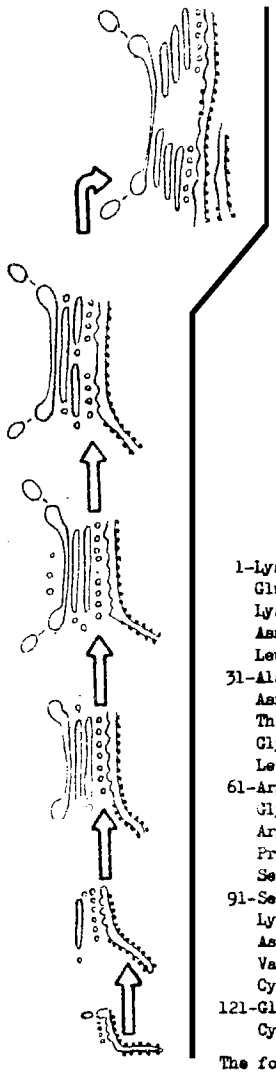
[94] We may, however, suspect that the above apparently preformationist ideas do not represent, in fact, anything more than a sort of terminological misunderstanding. As we will see later, the epigenetic, *"de novo"* appearance of complex forms cannot be interpreted in terms of *"de novo" creation.* An agency, a complex agency, is to be postulated in order to provide a scientifically acceptable explanation of epigenetic phenomena. If that is the meaning of Bonner's, Holtzer's and Waddington's claims, their opinions do not explain away the observational evidence for the existence of epigenetic transformations, or differentiation, but simply integrate in one expression both the phenotypic and genotypic aspects of life.

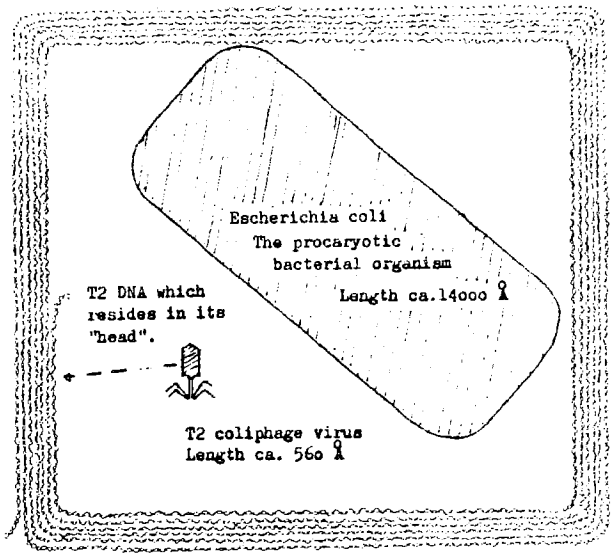
have to be considered rather as a sort of mnemonic technique, which does help to form the concept but does not represent it properly. Let us illustrate this rather important point by the example of the functional differentiation of the nematocyst, which is a sort of small projectile. It may be shot out by coelenterates to pierce and paralyze prey. "In 100 species of coelenterates related to Hydra, 17 types of nematocysts have been described...Nematocyst release occurs when the cell is stimulated by the appropriate chemical and mechanical stimuli, such as might result from the presence of the small organisms used as food..." (Novikoff § Holtzman, 1970/213). Nematocysts constitute one of several possible forms of epi-genesis which start with the so-called interstitial cell. An interstitial cell, in fact, may "differentiate into a nerve cell, a cnidoblast, or a sperm cell, or else grows and divides without differentiating" (Berill, 1971/ 134). The conversion of a cnidoblast into a nematocyst is represented on Fig. 5.2.

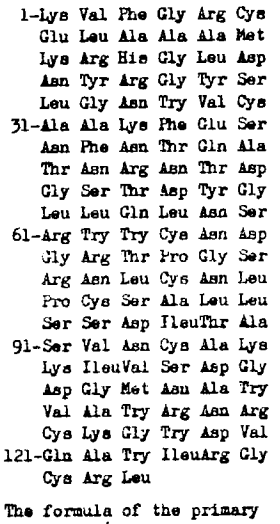
We observe the process of differentiation of the nematocyst within different ranges of the observational scale. We may observe the structural changes of the cell as a whole, we may concentrate on transformations of specific cellular organelles, such as the endoplasmic reticulum or the Golgi apparatus, or we may descend to the level of biochemical processes, during which some special poisons, the molecular details of the stylet and of the triggering device and so on are produced. We cannot observe all these events at the same time. Fig. 5.2 represents the highest level of the observational range, in the process of the development of the nematocyst. This representation is two dimensional only, and is discontinuous. Fig 5.3 represents gradual stages of the epigenetic origin of the Golgi apparatus, which undergoes extensive changes during the differentiation of the cnidoblast.

> "The Golgi apparatus.. .becomes highly developed as the cell begins to secrete the proteins that are stored in the nematocyst...[the development] begins as a Golgi vacuole, small at first and then enlarging greatly. Innumerable small vesicles develop from the much enlarged Golgi saccules and fuse with the nematocyst...When the nematocyst attains its maximum size, the ...Golgi apparatus regress, breaking into vesicles which progressively diminish in number...The striking development...of Golgi apparatus, followed by its virtual disappearance is but one of the interesting features of cnido-blasts..." (Novikoff and Holtzmann, 1970/213-4).

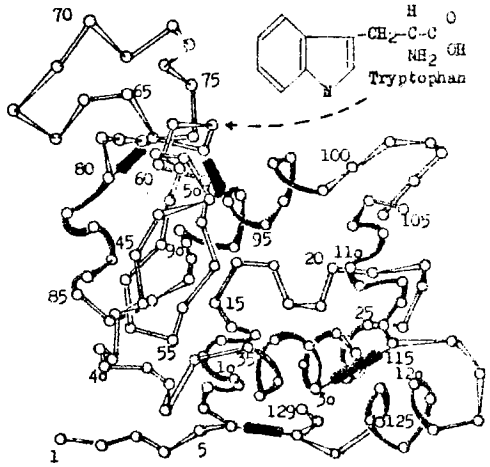
The real process takes place in three-dimensional space and is continuous, so that only a film might rep-







The formula of the primary structure (aminoacid sequence) of lysozyme.



A model of the secondary (helical and non-helical segments) and tertiary (the folding of the"backbone") structure of egg-white lysozyme.

Fig. 5.1 Schematic representation of the origin of Golgi apparatus. (After Morre et al. 1971, fig.14).	Fig. 5.4 Bacterial cell, virus molecule, viral DNA molecule, polypup-tide molecule, aminoacii molecules drawn at..roughly speaking,the same dimensional scale. (Upper part after Herskovitz 1973, fig. 3-13; lower part after Reithel 1967, fig.22.1)

resent it properly. But even a film could not show the epigenetic processes which take place on the molecular level. Of course, fragments of the development of the nematocyst, fragments of the differentiation of the Golgi apparatus, might possibly be filmed, if a device capable of doing it were

imaginable. But the observational impossibility we are talking about means an absolute incapacity of the human senses to integrate simultaneously the events which are observable separately on the different observational scale ranges. The real process takes place simultaneously on all these different observational scale ranges. So the representation of the actual process is reconstructive, and probably mental, not pictorial, in the ordinary sense of the word. For instance, an astronaut may be able to see the whole Earth from his space capsule, but if he wants to see the details of, let us say, Westminster Abbey from this astronomic distance, he has to use a telescope, and at the same time he loses the view of the whole Earth. In the same sense, the molecular, biochemical processes of differentiation simply cannot be observed simultaneously with the microscopic events.

When we are talking about a functional event and its developmental origins, we oannot limit ourselves to a single observational range, to a single level of description. The functional "units" in fact, usually have a multi-level or multi-dimensional organization. The functional release of energy by an ATP molecule belongs to the molecular level of events, but the functional mechanical response of the spermatozoon's tail is observable, and it "belongs" to a higher organizational level. Similarly, a single heartbeat constitutes, undoubtedly, an example of a truly functional event but consists of an integrated complex pattern of structures and dynamisms which are observable on the macroscopic level (e.g., the function of papillary muscles which control the closure of the heart valves), the microscopic level (the propagation of electric stimulus along the septum, the contraction of myo-fibrillae) and on the molecular level (the release of the energy by ATP molecules) . (See similar considerations by Beckner, 1959/120).

Therefore, the concept of differentiation in biology constitutes a purely mental idea of reality which cannot be represented by any of the known graphic aids. The distance between the molecular and the cellular levels of observation absolutely transcends the capacities of the human senses, even in the case of the smallest bacteria (see Fig. 5.4).

In other words, adequate concept of biological epigenetic events can be communicated only part by part, level by level. The details of sperm-

atogenesis and ATP-genesis which we are going to discuss in the next sections of this study do not represent anything more than a fragmentary account of the real event. Spermatogenesis is described on the cellular level, without entering into the molecular transformations which underlie it. ATP-genesis, on the other hand, is described on the molecular level, practically without mention of the nature of the greater context which determines the successful formation of ATP molecule. In the latter case we refer to this context by means of shorthand expressions such as "environment" or "environmental parameters," but the nature of these parameters is also known only fragmentarily.[95]

We might say that the complexity of biological structure and dynamism creates a special kind of epistemological problem for the human mind. The observational pattern is repetitive, dynamically "logical," even on the level of molecular details. This produces a sort of temptation to treat a fragmentary piece of evidence as a sort of unit. On the other hand, the multidimensional complexity of the whole "life cycle," which is the only non-arbitrary unit of life phenomena, discourages the efforts of the imagination. The previous discussion of the functional event might seem too complex to be clear, but now we are entering into the intricacies of the developmental processes, and the effort of imagination has to be even greater. It is easy to understand the functioning of a car, but the complexity of its production is hardly imaginable to an average mortal. We have to be conscious of these difficulties and not surrender in the face of the problems.

5.4 Spermatogenesis — an example of intraaellular differentiation

The spermatozoon is the result of directly observable transformations of an undifferentiated, apparently "ordinary" (from the structural point of view) cell, called a spermatid. The cell becomes elongated, its nucleus shrinks and its shape becomes characteristic to the species to which the organism belongs. Two small cytoplasmic bodies, called "centrioles," move toward the cell surface and one of them gives rise to a small cilium-like outgrowth which will become the axial filament of the future tail.

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[95] A clear and detailed analysis of some practical obstacles which are inherent to the process of empirical description in contemporary biology may be found in Luft (1971/20-22).

The centrioles move inward again close to the nucleus, drawing the filament and a pocket of the adjacent cell membrane with them, so that the filament in reality becomes external to the cell. Subsequently, the active centriole returns to the cell membrane, carrying the membrane fold with it. Mitochondria develop in the vicinity of the filaments' basis, while the other centriole produces the ring of the nine fiber sets which thicken the central part of the tail. (Cfr. Berill, 1971, p. 198-9). Many other events take place before the spermatid achieves its final shape. We have limited ourselves to those events which are related directly to the locomotory machinery. From figure 5.3 it is rather obvious that as the result of the transformation, the originally round spermatid becomes similar to a tadpole, and the adaptation of its shape to the voyage it must undergo is evident. The course of the above-described process of differentiation gives an answer for the question of the functional structure's origin. In the light of observation of gametogenesis, it is not only obvious that the functional structures appear "de novo," but the detailed picture of this "de novo" appearance phenomenon may be observed directly or at least reconstructed from the details.

This process has some characteristics which are analogous to the functional process analyzed in the preceding section. The transformation of the ball-like spermatid into the tadpole-like spermatozoon is a highly repetitive process, being exactly the same in any other differentiating male gamete and is curiously lacking in events which are not related to the final effect, namely, to the functional structure of the spermatozoon. In a sense the course of events seems to be *minimal* or close to minimal. It means that the transformation of the spermatid into the spermatozoon apparently follows the "shortest" way of change. The transformational events may be described in terms of purely chemical processes, such as syntheses, lyses, influences, changes, dislocations, movements and so on. The question arises whether the process of the gradual de novo appearance of the functional structures, that is, the process of the differentiation, is reducible to these physico-chemical dynamic states. In the case of the functional process, we have seen that reducibility may signify two different'concepts. One is the concept of the distinct descriptive elements which are necessary and sufficient to reconstruct in our mind the reality of the functional process: we may call this concept *reducibility of the details*.[96] The other sense of reducibility

[96] "Every analysis is in a sense a reduction, that is, a decomposition of a complex into simpler units and a disclosure of a mask of relations..." (Bunge, 63/11).

is related to the notion of divisibility. As we have seen, a process which fulfills the criteria of functionality is indivisible, as its integration is essential to its functional properties. So although the details of this process are physico-chemical, in the most ordinary sense of the word, they represent a sort of a "whole." This whole is not kept together by any "supra"-physical force, yet the system is functional only as a whole. The functionality is then a property of the undivided complex system.

Now the same distinction may be applied to the process of differentiation. Its details are describafale in terms of many different purely physico-chemical processes and so it is reducible to the physico-chemical reality, in the sense of the reducibility of details. Are those details correlated in a specific way within the process of the differentiation? The answer has two aspects. One is purely linguistic , the other reflects the empirical, observational reality.

From the etymological, purely linguistic, point of view, any process which leads to an increase of complexity, structural and/or dynamic, may rightly be called a process of *differentiation.* From the terminological point of view, it makes no sense to talk about a process of differentiation, or epigenesis, if we have to do with a static structure, or with a dynamic state which does not lead to an increase of complexity. The notion of a minimal epigenetic event together with the notion of the increase in complexity of a system was discussed at the end of chapter three.[97] A terminological "indivisibility" of an epigenetic event means nothing more than the essential irreducibility of a dynamic state to a static state, on the one

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[97] 'The conceptual difficulties created by epigenetic phenomena are well illustrated by the following text, which, although it refers to a past period of biological investigation, has nevertheless remained valid until now.

> "—The task of the epigeneticist was...formidable...Epigenesis is change building on previous change and in the normal course of events — it leads always to a demonstrable...end. ...that is, to the production of an adult organism belonging to a particular species. But the fertilized egg, these epigeneticists well knew, was truly unstructured and carried out quite independently a sequence of remarkable transformations. If, therefore, organic form is not original but is produced, what possibly can account for the regularity and directedness of such an extraordinarily complex developmental process? "To pose this question was, for the most determined epigeneticists, to anticipate its answer: they postulated the existence of a special developmental force..." (Coleman, 1967/42).

It is obvious that by denying the reality of epigenetic transformations on the phenotype level we remove that question, and a further search for the genotype's reality becomes unwarranted.

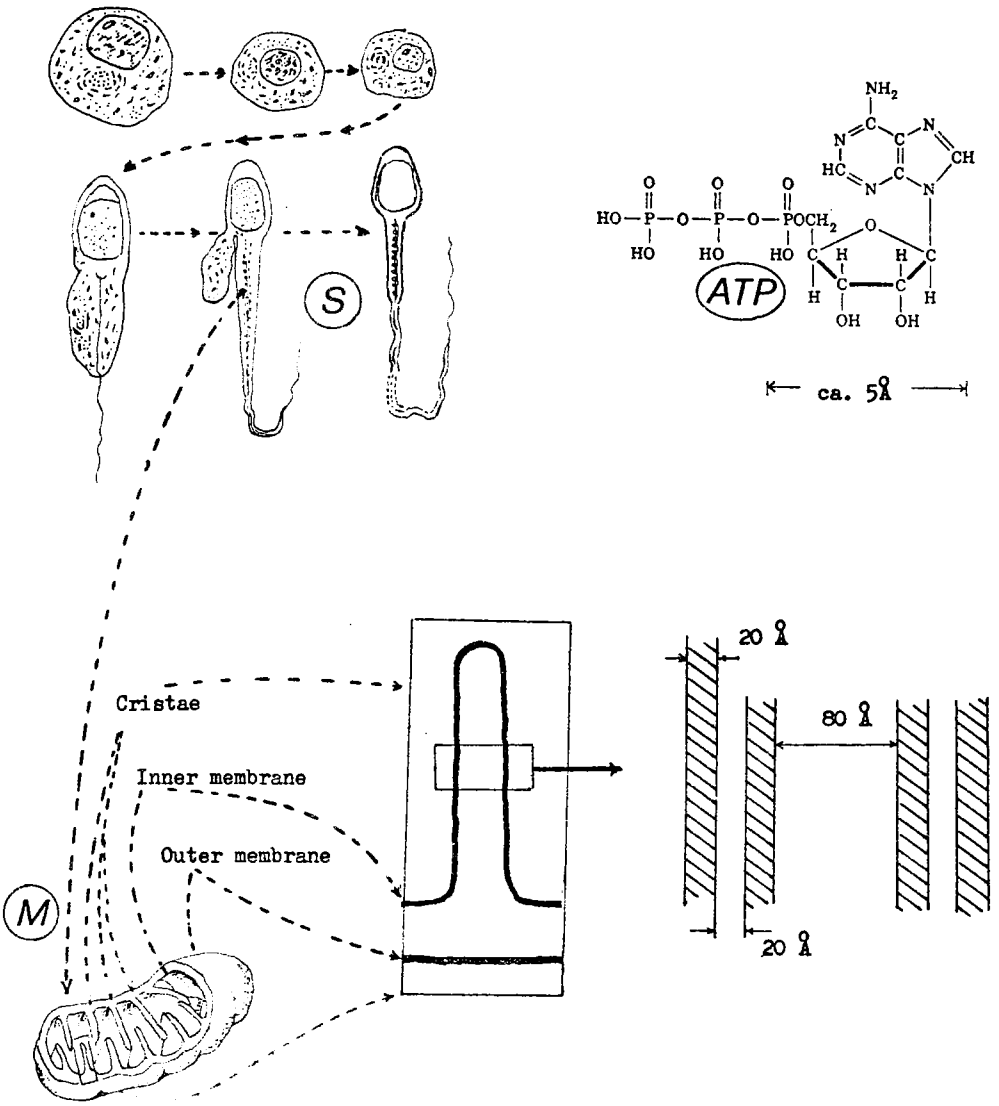

Fig. 5.5 Different structures of different dimensions constituting the functionally indivisible whole. S - Some developmental stages of spermatozoon (After Ch. Houllion 1972,fig.11); M - Mitochondrion and highly idealized representation of some of its details (After Yost 1972, fig.2.24) ATP - Schematic, two-dimensional representation of adenosinotriphosphoric acid.

hand, and a causal irreducibility of the repetitive epigenetic event to the intrinsic determinations present in the starting point of the event, on the other.

But during the life cycle of a living organisms we can easily recognize a form of differentiation which produces a *functional* structure. This type of differentiation, appearing repetitively, may easily be recognized and distinguished from other types of differentiation which do not lead to. the

appearance of functional structures (e.g., neoplastic differentiation, pathological growth, pathological development). The concept of non-functional differentiation lacks any definite, concrete sense. Any physical system which undergoes a change resulting in an increase of the descriptive complexity of the system is in a way *differentiating*. But living systems are characterized by a special kind of differentiation. This differentiation is a complex series of dynamic states which approach in a physically "shortest" way the state of functionality. We will call this type of differentiation the *developmental* differentiation. Developmental differentiation is repetitive and may be observed on the different levels of the organism's organization. Man's egg undergoes a differentiation which under normal, that is, non-pathological conditions, results in the functional state of the cardiovascular, nervous, hormonal, locomotory, digestive, excretory apparatus. Each of those complex developmental processes may be further (at least conceptually) decomposed into detailed developmental processes. For instance, the highly functional types of blood cells are products of the divergent differentiation processes which in one case lead to the appearance of erythrocytes, in others to the appearance of lymphocytes, megacaryocytes, blood platelets, amebocytes and so on. The developmental process is composed of successive transformations of successively more and more complex structures which, all but the last, are nonfunctional. The last one is functional. But what does this mean? Can we call a single static structure functional?

A minimal, "atomic" functional structure, as we remember from our previous analyses, is composed of at least two different separate structures. (For the sake of simplicity we do not mention all the environmental require-

raents which determine the efficacy and minimality of the functional reaction) . An epigenetic process, in order to generate a minimal functional structure, has to be composed of at least *two* different developmental pathways. This conclusion, of course, may be reached as a result of mental speculation on the fact of the repetitivity of functional events. However, direct observation of developmental processes, such as spermatogenesis, the differentiation of nematocysts and the like, provides us with direct evidence confirming the former, logically inevitable, conclusion.

5.5 The process of ATP formation — an example of a biochemical epi-genetie process

Before we generalize the results of our considerations on spermatogenesis, let us have a look at the details of another epigenetic process which is typical of all forms of living beings, even of the most "primitive," the process of the synthesis of the ATP molecule. This molecule, as we have seen in chapter four, constitutes a sort of universal energy store for the processes of energy transfer in living organisms. There are many ways in which ATP may be formed by a living organism from the mineral compounds absorbed selectively from its environment. We will discuss the process of ATP formation in its most rudimentary, general outlines.

ATP is composed of adenosine and three phosphate groups (see Fig. 5.5). Adenosine is a rather complex molecule (9-beta-D-ribofuranosyladen-ine) composed of a sugar molecule ?J-ribose)'coupled by a chemical bond (glycosyl linkage) with a purine called adenine. How do those complex molecules of D-ribose and adenine originate? The D-ribose molecule is produced from the glucose molecule which is the basic fruit of the photosynthetic processes. The conversion of the six-carbon glucose molecule into the five-carbon D-ribose molecule is achieved by a series of metabolic steps which have to be extremely precise, because numerous other pentoses(five-carbon sugar molecules) could be produced in this process. For the sake of simplicity we will confine ourselves to the details of the purine metabolism only. The purine molecule is built up in the following manner (see Fig. 5.6).

The phosphoribosyl-1-pyrophosphate molecule (PRPP) serves as the joiner's bench to which the gradually synthesized elements of the purine molecule are fixed. From the glutamine (one of the 20 basic aminoacids) the NH_2 group is attached to the 5th carbon atom of the PRPP. Then the whole glycine molecule (another of the basic aminoacids) is conjugated to the NH_2

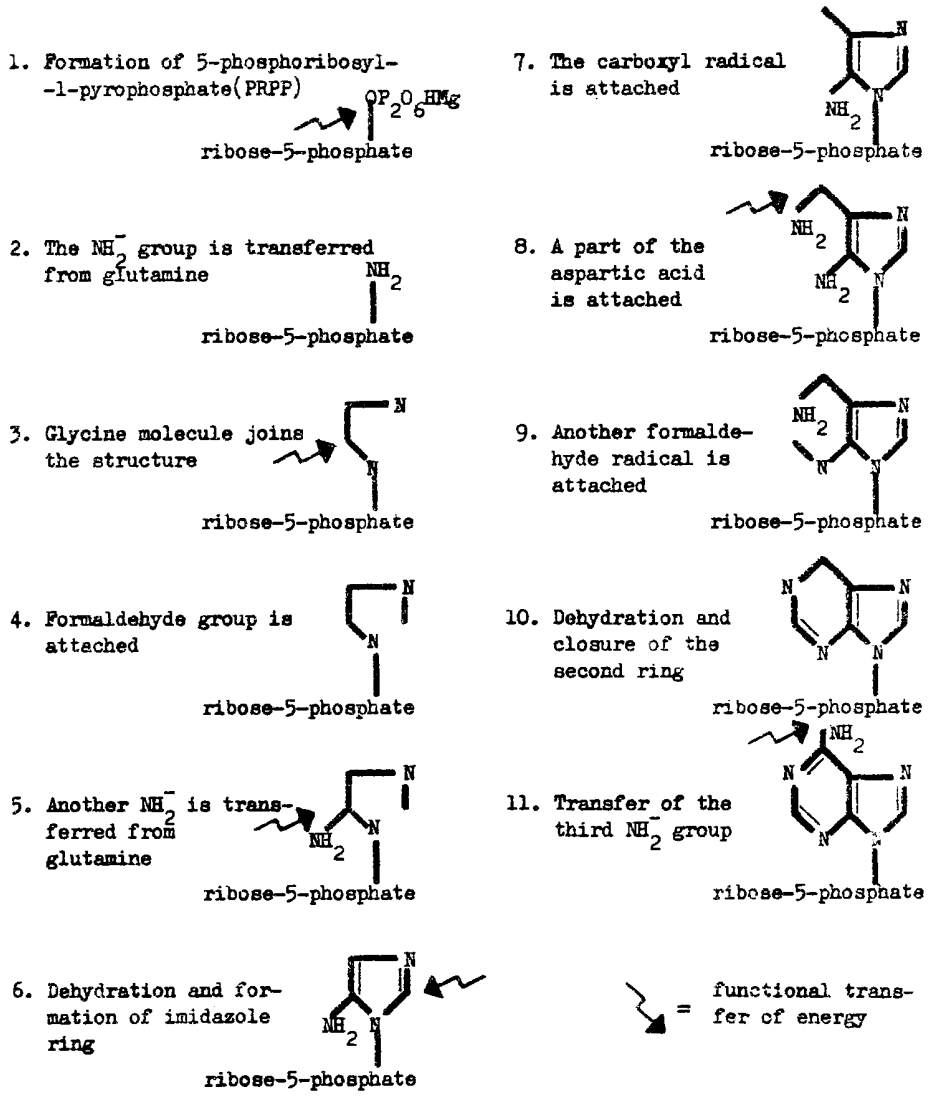

Fig. 5.6 Schematic representation of the epigenetic process which leads to the formation of adenylic acid (adenosine monophosphate or AMP) molecule. (See Reithel,1967/l68ff. and Mahler and Cordes, 1971/820ff.)

group. Here the molecule of ATP has to change into an ADP molecule, liberating the energy needed to produce this amide-type link. Now a specific enzyme (N^5 , N^{10} -methenyl tetrahydrofolate is the non-protein element of this enzyme) adds one molecule of the formaldehyde (CHOH).

The second molecule of glutamine aminoacid lends a new NH_2 group, and the ATP molecule has to break into ADP + P_i in order to drive this reaction against the thermodynamic equilibium state. As the purine molecule is composed of two closed rings, the "first" (imidasole) ring is already almost done, but its elements are not joined in a circle. This is achieved by a process of dehyration, in which one water molecule is "sucked" out from the ring components, and they "shrink," closing the gap and forming an uninterrupted chain, or ring, of five chemical bonds. This dehydration is also ATP-dependent.

A specific protein (phosphoribosyl-aminoimidazole carboxylase enzyme molecule) attached a $CQOH^+$ group to the imidasole ring. Then a molecule of aspartic acid "joins the club" with the help of ATP (which, as usual, breaks down into an ADP molecule + P_i, liberating the needed amount of energy at the right point and at the right time - like a soldering kit applied at the ends of two wires which have to be linked together). The aspartic acid (one of the basic aminoacids) is not needed as a whole for the production of the purine molecule, so that its "useless" fragment is cut off during the next synthetic step. Once again a formaldehyde molecule is attached to the "stump" of the aspartic acid molecule. And again the dehydration process takes place, so that the second ring is closed.

But the molecule of adenine is not ready yet. It remains to convert inosinic acid to adenylic acid in order to complete the synthesis of the purine ribonucleotide. A few enzyme molecules, a few more metabolic steps, and the purine is ready. (See Mahler and Cordes, 1971/320-4; Reithel, 1967/ 168-176).

The last schematic chemical formula of Fig. 5.6 represents adenylic acid, which is also called adenosine monophosphoric acid (AMP) (See Fig. 5.5). It may be phosphorylated once, to form ADP, and then again, to be converted into ATP. This process requires a relatively high energy release. The energy is provided either directly by photosynthetic processes or by the oxidative processes which usually take place in mitochondria.

The list of the precursor requirements for the synthesis of a single molecule of AMP includes at least twelve different enzymes and quite a number

of smaller compounds. It is worth mentioning that the adenine molecule

> "can arise from a potpourri of ammonia and carbonate reacting in an ultraviolet discharge; hence we can assume that its structure is thermodynamically probable" (Reithel, 1967/175).

In spite of this fact, AMP molecules are produced by living organisms in the complicated and strictly ordered way described above. Each step of the synthetic procedure is rigidly controlled so that

> "it may be assumed that the complexities evident in this description are dictated by the need for control" (Reithel, 1967/176).

The term "need" may provoke some teleological connotations. We should not be impressed by the above statement. From the point of view of our analysis it is not relevant whether there is any "need" for an ATP molecule or not. What is relevant is the fact that the process of ATP formation is obviously epigenetic and repetitive. It is not, however, a functional process. Only its very final stage, the energy-loaded ATP molecule, may constitute part of a functional system, on the condition that another structure capable of absorbing this energy in a functional way is also produced.

5.6 Some additional remarks on the evidence concerning biochemical and anatomical phenomena of development

Only a chemist can appreciate the extreme precision of the processes just described. Some more important features of the process, from the philosophical point of view, have to be put clearly

a) The process just described is only one arbitrarily selected example of the literally thousands of chemical reactions which go on intermittently in any living being, starting with blue-green algae and ending with whales.

b) The process of the purine molecule production was described here only in its most essential details, but the real story is ten or a hundred times more complex. In other words, in order to produce the purine molecule, the above prescription is not sufficient. The pH control, the ions concentration control, the temperature control, the separation of the various interacting molecules engaged in the whole process, the energy barriers created or abolished in order to keep the growing molecule together, or, on the contrary, to dissolve the internal links which prevent the atoms from falling apart, the control of the strict succession of the synthetic steps and elimination of the danger of attachment of the "building bricks" to incorrect parts of the purine molecule -- all this was not even mentioned in the above "analysis." And we have to add that many of those elements are not yet as clear as we may wish them to be.

c) The fragmentary nature of our present knowledge, however, does

not detract anything from the concepts of epigenesis, repetitivity or development. We might say that in the light of the presently available evidence, the biological and biochemical processes we were discussing are *at least* as epigenetic, as repetitive and as developmental as we know now; though future observations may increase this awareness of the order and the precision, they cannot weaken it.

e) In biochemical terminology, the different forms of the "growing" purine rings are called "precursors" of the ATP molecule. We miglit say, mutatis mutandis, that blastula, morula, gastrula, neurula and other embryonic stages of the life cycle are "precursors" of the functional stage, which is called the adult stage.[98] Of course, during the purine synthesis, many functional events intervened, and, in fact, the whole process was functional, but the processed molecule was not. The purine rings are developing, not functioning. The process of the synthesis is not developing but functioning. Later on, the ATP molecule will be functioning -- but its functioning is the result of development. The same mutatis mutandis, may be said about all the other enzymes, aminoacids and sugar molecules involved in the process of purine synthesis. Before they started functining in this process, they had to develop, had to be organized together in an orderly functional system which was able to produce purine molecules.

5. 7 The nature and the concept of the developmental event

In order to facilitate the application of our analyses to the discussion on the nature of genotypic agency, we will try now to generalize the essential elements of the developmental event.

The concept of the "functional structure" is the main category which determines the criteria of distinction between developmental and non-developmental events. The epigenetic process, in fact, may lead to a set of highly differentiated, complex structures which are not functional. This non-functional epigenesis may be illustrated by the case of teratomas.

A teratoma is a sort of tumor or neoplasm, whose origin depends on

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[98] "...[because] the adult phenotype is the result of a series of developmental steps, a structure should not be defined as the form at a single stage of the life-history. Rather it should be represented by the whole sequence of forms that make up the ontogeny: more accurately, it should not be defined as the forms but rather as the sequence of the series of changes that underlie the change of forms..." (Chan, 1970/67-8).

Sir Kenelm Digby (1644) in the following way describes the epigenetic process and the step-by-step formation of the "precursors":

> "...all generation is made of a fitting, but remote, homo-geneall compounded substance upon which outward Agents, working in the due course of Nature, do change it into another substance, quite different from the first, and do make it lesse homogenall than the first was. And other circumstances and agents do change this second into a third, that third, into a fourth; and so onwards, by successive mutations that still make every new thing become lesse homogenall than the former was,...until that substance bee produced which we consider the period of all these mutations..." (quoted after Needham, 1959/121).

the proliferation of undifferentiated, immature cells. So the process of teratoma formation starts with a set of observationally homogeneous cells. During the growth of the tumor the cells become more and more differentiated producing an impressive number of heterogeneous structures.

> "In general the varied components are combined in a disorderly fashion...Some portions of teratomas are highly organized so as to form, for example, well formed digits with nails, phalanges and metacarpals teratomas [however] have no true organs or body regions; they have scattered patches of central nervous tissue but no brain, renal tissue but no kidney, teeth without a mouth and so on. Teratomas have also anomalous multiplicities of various tissues as, for example, hundreds of teeth...In summary teratomas owe their complex structure to divergent differentiations...but the basic organization is lacking..." (Foulds, 1969/206-7).

We may replace the term "basic organization" by "functional structure," in the sense we have defined earlier. In teratomas the epigenetic process does take place, for different extremely specialized cells, and even special complex parts of organs, teeth, for instance, are produced. What is lacking then? The pathological epigenetic process is composed of unrelated developmental paths. There is no adequate integration between the final results of the different, heterogeneous epigenetic processes.

We may try to construct a minimal concept of functional, or developmental, epigenesis. It may be represented schematically in the following way:

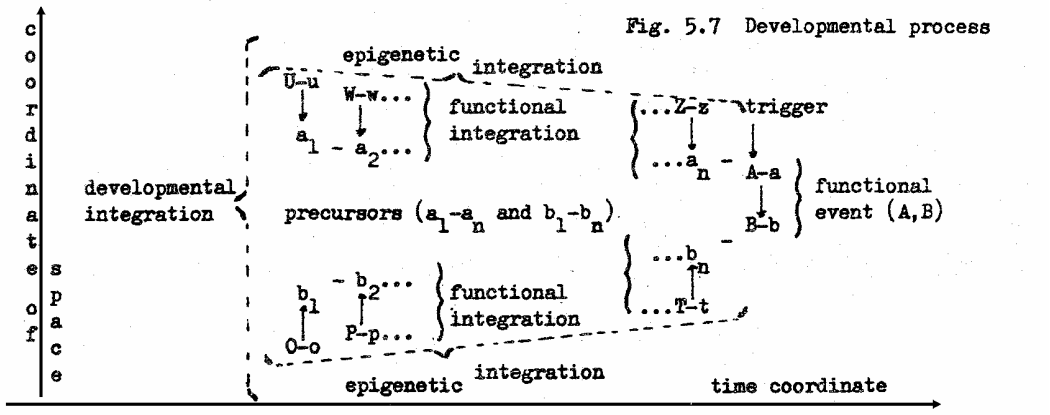


Fig. 5.7

Developmental process

The above figure (fig. 5.7) represents two epigenetic processes during which the functional structure A, B is gradually formed from the respective precursors. The vertical arrows represent the dynamic functional relationships within the functional systems. The final functional event triggered by an environmental stimulus is prepared by two sets of successive functional events (U-a_1, W-a_2, ...Z-a_n and 0-b_1, P-b_2,--.T-b_n respectively). It is rather obvious that at least two different epigenetic events, more or less complex, dependently of the nature of the final functional structures, must be engaged in the production of an atomic functional event.

5.8 The levels of integration implied by the abstract notion of the developmental event

Now we can recognize three different "levels" of *integration* within the minimal developmental event described above.

The first level, which we may call "functional integration," is reducible to the same set of conditions we have discussed in analyzing the concept of an "atomic" functional event. A specific spatio-temporal pattern constitutes a necessary premise of the functionality of each successive event which takes place during a single epigenetic path, whether developmental or not. If we want an example we can reconsider the separate steps of the construction of the purine molecule (see Fig. 5.6). Most of them relied on the energy transfer between different structures, and this energy transfer was functional.

The second level of integration, which we may call "epigenetic integration," consists in the actual indivisibility of an epigenetic path taken as a whole. Of course, there is no need to treat this indivisibility as a sort of *intrinsic* property of the set of functional processes which constitute a given concrete path. On the contrary, these processes are not physically indivisible. But in the case of the developmental process, and especially in the case of the repetitive developmental processes, this "epigenetic integration" has to be considered both as a logically necessary condition and as a more or less directly observable fact. From Fig. 5.7 it should be quite obvious that the term "epigenetic path" refers to three different interrelated sets of entities or to the totality of them. The first set of entities consists of the *non-coexistent* series of structural stages, or "precursors," of the final product of the epigenetic path. The second consists of the presumably functional structures which participate in the sequential transformations

of the "precursor." And the third is composed of all the non-randomly organized "environmental" structures and other physical parameters which determine and condition the functionality of the processes involved in the transformations of the "precursor." The second and third elements of the epigenetic path are divisible (conceptually) into "atomic" functional systems, which are necessarily separate in time, and most probably also in space. We will call the first series the "passive" element of the epigenetic path, while the other two sets will be referred to as the "active" element of an epigenetic path.

Finally, the third level of integration we may call "developmental integration," which is also recognizable both speculatively and empirically. We may postulate it speculatively as a purely physico-chemical condition for the "de novo" appearance of two distinct structures which form together an "atomic functional structure," and we may recognize it by comparing the normal course of developmental processes with pathological, neoplastic epigenesis.

There are some important differences between these three levels of integration. The first level of integration exists between the coexistent structures, while in both the latter cases the integration is to be supposed between the non-coexistent structures. So both epigenetic and developmental integration has to be conceived as a *"trans-temporal"* form of integration.

The epigenetic form of integration refers to structures which, not being coexistent, may, however, at least, theoretically, be confined to the same spatial "department," to put it roughly. In the case of the developmental integration this is physically impossible. For this reason we are forced to conclude that the developmental integration postulates both trans-spatial and trans-temporal form of integration.

The above three forms of integration may be considered as a sort of entitative and explanatory hierarchy. What does this mean?

The efficacy and economy characterizing a functional event might have been explained in terms of a random integration if it were not repetitive, but because it is repetitive it has to be explained by a non-random epigenetic process. But a non-random epigenetic process is not sufficient to provide an answer for the non-random origin of the simplest "atomic" event, for this event necessarily presupposes an integration of the developmental kind. A random case of a developmental process is, of course, physically possible, but the repetitivity of a functional event necessarily postulates

the non-random form of developmental integration.

In this way, we have come to the conclusion that some phenotypic phenomena postulate a sort of integrative agency. The integration we are talking about is to be conceived as a *trans-spatial,* and simultaneously a *trans-temporal, constraint* which eliminates, in one way or another,an extremely high number of other molecular reactions, organellar transformations or cellular interactions, which are not only *physically* possible, but which actually appear here and there during pathological conditions. All pathology, in a way, might be conceived as vast illustrative evidence for the dynamic states which, because of some intrinsic or extrinsic reason, have been liberated from the influence of this constraint.

The above analysis and description of a developmental event, and of a developmental *system* (this word may signify the whole ensemble of different sets of entities involved in the developmental process) was made in terms of purely physical, or physico-chemical, concepts. Of course, it was represented in an abstract way, but, according to the physico-chemical nature of a given functional system, the respective developmental system may be described in terms of concrete material entities composed ultimately from single atoms or inorganic molecules. The developmental system is not determined by the functional structure it produces. The repetitivity of a functional event, however, postulates a non-random organization of the developmental system. As in the case of an "atomic" functional event; the observed efficacy and iso-thermy of the processes involved in the "active" element of the epigenetic paths which form the developmental system postulate the functionality of the single events which mould the precursor, the "passive" epigenetic path. All this, in turn, requires the non-random pattern of the intrinsically heterogeneous (spatially and temporally) environmental" sphere (see Weiss P., 1967/ 805).

We may now agree with Beckner, Braithwaite, Sommerhoff, Nagel, Feigl and Brodbeck that a developmental system does not presuppose any metaphysical doctrine of final causes. We may agree that although the functional structure constitutes the *last* product, with reference to the time coordinate, of the developmental system, the system as such "is simply a special case of a physical system in the ordinary sense of that term, and can be described...in a vocabulary suited for the description of nonteleological systems" (Beckner, 1959/132). But the repetitivity of developmental systems observed in the case of the continuity of "life cycles" constitutes the

explanation of the repetitivity of functional events in a very restricted sense of the term "explanation." The repetition of development events produces a new sort of empirical evidence, and it carries a new "question-raising" problem, namely, that of trans-temporal and trans-spatial constraints .

Of course, the whole empirical evidence is *heterogeneous,* and the concept of the development or of the function cannot be *homogenized.* The development, or the synthesis,of every kind of molecule is different, and it has to be different if physical laws are to be obeyed. The development cannot go on without *different* functions, *different* functional events, *different* functional chains. The heterogeneity constitutes an intrinsic postulate of physico-chemical description and of physico-chemical understanding of the life processes. Those processes are repeatable in a way which suggests and postulates the utmost precision of the events, down to their molecular level. We have seen that functional events constitute a sort of automatic spontaneous, or "mechanistic," events triggered by the environmental influences. But the developmental events constitute a physically indispensable condition of the origin of the functional systems, and the repetitivity of the developmental events is not only a postulate for the repetitivity of the functional events but is also a more or less directly observed fact (see Noll, 1965/105; Oparin, 1961/104). This fact is now observed upon various dimensional levels of the organism's structure, from the level of the whole organism down to the level of the specific metabolic pathways producing dozens and hundreds of organic molecules.

Those developmental events are supposed to have their ultimate explanation in the genotype's reality. The intrinsic irreducible heterogeneity of the developmental processes postulates an adequate heterogeneity of the genotype's activity. Any theory of the entitative nature of the geno-typic agency should respect this fundamental postulate.

5.9 The trans-temporality, trane-spatiality and divisibility of developmental events

One of the characteristic properties of the functional event is its entitative indivisibility. Every truly functional event is intrinsically "quantic," which in physiology is often referred to as the "all-or-none" law (see section 4.9). This fact is quite understandable in terms of the *coexistence,* integrity and minimality of the structures which determine the conditions for the effective and functional, that is, non-superfluous transfer

of energy. We may ask now to what extent and in which sense a developmental event is indivisible.

A series of developmental events, that is, functional chains which form the sequence leading to the appearance of a functional system --an eye, a microfibrile in the functional state, an enzymatic complex in the functional state, and so on, may be physically *minimal* or *redundant*. It seems that, in non-pathological circumstances, the available evidence suggests that the developmental events observable in the living body are minimal from the physical point of view. The time range of an event is a sort of indicator of the efficacy and economy of the process. The results of an athletic competition, for instance, its efficacy, are measured in terms of the minimal time, and calculations of the efficacy of the physical processes underlying an Olympic triumph show that this efficacy is rather close to the physically conceivable maximum. It is quite possible to run slower, to walk the Marathon distance at a snail's pace. But it is impossible to halve the time of the Marathon race. In the same sense we may say that the actual, non-pathological process of embryonic development, or, more generally, of any life cycle, is strikingly close to the minimal time range. Elsdale generalizes the empirical observations on the pattern of the developmental events, concluding that they are "inherently precise." And he continues:

> "On the view that all morphogenetic processes can be considered as inherently precise processes, the function of the genome in morphogenesis is tp specify the rules governing mutual cellular constraints in each temporal and spatial compartment of development" (1972/107-8).

It would be difficult to imagine, in the light of our present knowledge of the biochemical processes, a more economical process for the construction of functional structures than the one which actually is observed within the living body.[99] Does this mean that developmental events are characterized by the "all-or-none" property? Yes, they are, but the meaning of this property is more *analogous* than literal. A given series of events constituting a given "atomic" developmental event has to be completed if its final functional result is to be produced. In 'this sense

[99] The intrinsic precision of developmental events may be illustrated by the fact that if a halved embryo produces two complete organisms, the number of cells in the adult forms is the same (Schjeide § De Vellis, 1970/9). Of course, such a statement is only approximative, for it is neither easy nor even practicable to count all the cells in a living multicellular body.

the uncompleted series does not produce the final result and so the property of "all-or-none" enters here in the similar sense in which it has entered the case of functional events (see Weiss,. P., 1961/23).

The developmental processes are expected, and are also observed, to produce the physically necessary constraints, such as limiting membranes, specific concentration of different ions, specific spatial relationships between different molecules...and so on, which make some event physically inevitable, efficient and minimal at the same time. Now, any redundant, that is, non-minimal, structural result of the developmental processes would lead to impairment of these functional events. It would either destroy their efficacy, because they are minimally efficacious, or would make them over-efficacious, i.e., the released and wasted energy would not be minimal.

Yet the separate, intrinsically indivisible functional chains participating in two different series of developmental events, being physically independent, do not have to be so strictly organized in space and in .time. They can be divided. They can be divided simply because they are already separated in space. The artificial division inflicted by experimental procedures may happen to go along the actual, "natural" line of this spatial separation (see Bonner, 1963/4; 1965/127-8; Berill 1971/469-70). This seems to be the correct explanation of the rather strange fact, which is however a commonplace in developmental embryology, that the primordia of an organism, before they reach full integration in the adult, functional form, are relatively independent from other parts of the developing system. And in this sense the "all-or-none" property of developmental events should not be conceived with the same "rigidity" as in the case of functional events.

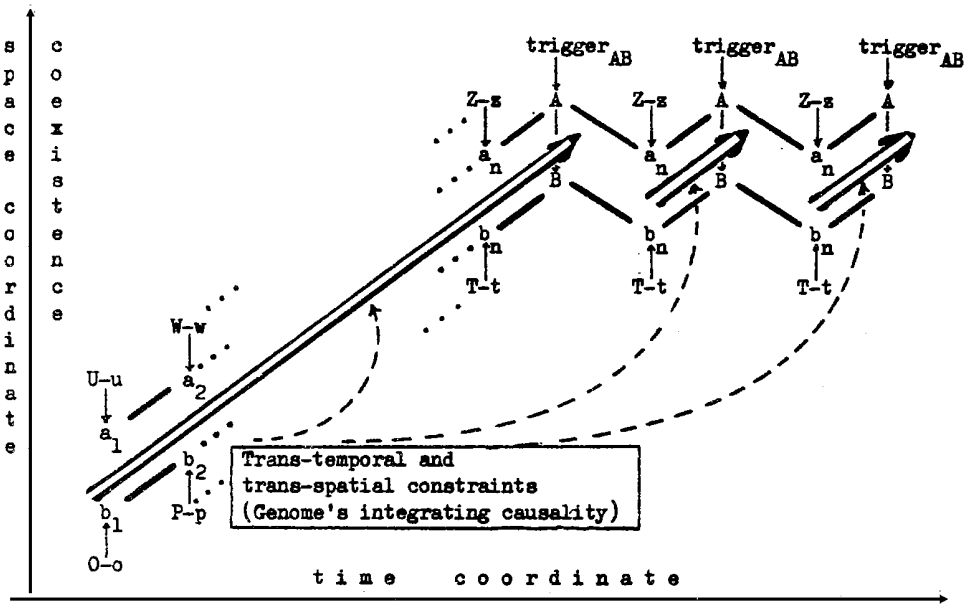
All this may be simply deduced from the concept of the trans-temporality and trans-spatiality of developmental events. Different parts of the final, functional structure are under construction in necessarily different spatial compartments, and the "timetable" within every single different epigenetic pathway is different too. If any external or intrinsic cause delays the epigenetic process in one part of the developing structure, it does not destroy the chance of reaching the final result but only produces an obstacle which may be overcome, provided that an appropriate regulatory agency intervenes before it is too late.

5.10 The developmental process and the notion of the anaplerot-ic event

Discussing the easily observable repetitivity of some functional

events, such as the locomotory movements of the flagellum, we have noticed the essential, intrinsic irreversibility of the functional event and the necessity for a correct conceptual framework to guide our search for an adequate explanation of this basic phenomenon of life. We have discussed two alternatives, the "epigenetic" and the "energy storage." Now, if every functional event produces a non-functional structure, composed of two elements, we may ask whether these two non-functional elements could not be converted back again into the functional ones, without the need of producing the whole functional structure "de novo" from the inorganic matter.

Fig. 5.8 A model of the anaplerotic event.



In some concrete cases it may happen that the structures produced as the result of a functional event are identical with the "precursors" of the functional structures. If it were so, they might have been used, "recycled," again. The return to the functional state would be identical, in that particular case, with the repetition of the ultimate part of the developmental event (see Fig. 5.8). We might call this part of the developmental process the *anaplerotic* event (or process). The repetitivity of a .functional event might be thus explained in terms of the repetition of the final part of the developmental event. This does not, of course, explain how the developmental process is possible. It

calls for explanation in terms of the genotype's agency. However, it reduces the heterogeneity of the whole set of evidence to be explained. Like the previous hypothetical speculations on the phenomena of repair and regeneration (see section 3.17), the model of the above anaplerotic system reduces the "quest ion- raising" empirical element of the theory to a fragment of the whole life cycle's phenomena, and the "question- solving" concept is consequently reduced to the notion of the genotype.

5.11 A summary of the question-raising elements of the life cycle phenomenon, or total phenotype

We may summarize the results of our analyses in the following scheme :

	Forms of dynamism	**Examples**	**Question-raising element**
A.	Functional event (trans-formation of the functional structures of a functional system into an intrinsically non- functional state)	Electron transport system, functional hydrolysis of the ATP molecule, transmission of the action potential in the nerve fiber, heart contraction … etc.	Repetitivity[100]

This form of dynamism is explained by the process of formation of the functional structures. The functional event is reducible to the functional structure and the environmental triggering influence. The question-raising element is explainable in terms of the epigenetic, developmental process.

B.	Developmental event (production of at least two different structures which form together a functional structure)	Biosynthetic pathways, "basic" and "adaptive" elements of life cycle phenomena	Repetitivity Trans–temporal constraints Trans–spatial constraints

This form of dynamism is to be explained by the idea of genotype agency his form of dynamism is to be explained by the idea of genotype agency, which is self-reproducing (auto-catalytic) , and which introduces trans-temporal and trans-spatial constraints controlling the random influences between the molecular, cellular and possibly higher, forms of bodily structures (hetero-catalysis). In other words,the developmental events are *reducible* to the idea of the *genotype.*

C.	Epigenetic origin of "individualizing" traits (production of structures which structurally characterize a species, a race, or even the single individual life cycles}	Epigenetic path of Antigenic structures, “species specific” non-functional (morphologi-cal) characteristics such as finger-tip pattern, pigmentation pattern…etc.	Repetitivity Trans–temporal constraints

[100] The element of order in the sense of repetitively (although the term "re-petitivity" was not explicitly used) and its crucial importance for the scientific, interpretation of empirical phenomena, was stressed by several authors. Monod, discussing the specificity and function 'of protein molecules, states: "Without order, without symmetry, science would not only be dull: it would be impossible" (1969/27). Polanyi considers "our capacity to distinguish coherence from randomness [as] an undefinable ultimate power of the mind.” Fatmi and Young, starting with observation of computers, conclude that intelligence “is that faculty of mind, by which order is perceived in a situation previously considered disordered” (1970/97). At the same time we should not thet if our conclusions correspond to the facts of biochemical reality such remarks as that, for instance, “the randomness of behavior of the units involved at one level does not necessarily depend upon the randomness of the units at lower levels of organization … the statistical laws that describe random behavior are irreducible” (Glass 1963/241), have no applications in biology.

> This form of dynamism is also expected to be explained in terms of the heterocatalytic activity, that is, the constraints, of the genotype. However, the trans-temporal form of constraint seems to be sufficient in the case of the epigenetic origin of the "individualizing" traits.

Bearing in mind a clear idea of the "question-raising" evidence collected on the level of the phenotype, we may now turn our attention to contemporary ideas and theories concerning the nature of the genotype.

Analyzing the phenotypic hereditary traits we have realized that "Dynamic process is the foundation of static form, rather than the reverse" (Weiss, 1961/24). The energy for these dynamic processes is provided by the non-animate environment, principally by randomly "organized" quanta of light energy. This energy becomes ordered in time and in space. It is utilized then to produce a relatively narrow set of structures which continue the process of energy utilization. This whole dynamic process postulates types of constraints, which are theoretically irreducible to the above "question-raising" empirical evidence.

CHAPTER SIX

EXPLANATION OF LIFE PHENOMENA: THE CONCEPT OF THE GENOTYPE

6.1 The "question-solving" element of genetic theory

In the previous part of our study we have tried to abstract these essential properties of phenomena of life which constitute the "question-raising" evidence of modern genetic theories. We have tried to define more clearly the concept of epigenesis (sections 3.20 and 3.21), the concept of functionality (section 4.9), the concept of different forms of integration implied by the notion of developmental epigenesis (section 5.8). We have seen that the above concepts necessarily postulate a non-random causal explanation. Because, principally, of the repetitivity of the functional, epigenetic and developmental events, the postulate of a non-random, causal influence becomes inevitable. This sort of influence is commonly attributed to a special entity called the genotype (section 2.6). In this part of our investigations, we are going to analyze the intrinsic theoretical structure of the genotype's idea and to discuss the validity of some criteria which determine the entitative properties of this postulatory causal agent.

In the present chapter of our study we try to distinguish and make explicit some elements which constitute the idea of the genotype. It seems that five different and relatively independent postulates participate in forming this complex idea. Some of them refer to the directly observable *effects* of the genotypic influence in the sphere of the phenotype, others refer to the intrinsic, entitative properties of this agency. The postulates themselves are complex. The most important, non-empirical element which underlies the origin of these postulates is the conviction about a certain adequacy between the causal agent and its effect. As a whole, the Postulates of the genome (genotype) represent a point where meta-scientific beliefs or generalizations meet with the empirical observational evidence.

This mixed origin of Postulates makes understandable some inter-pretational trends in modern genetics. The analysis of the Postulates will prepare a background for the further critical evaluation of modern theories which identify the genotype's agency with some structures or processes observable in living cells.

6.2 The basic premises of the concept of the genotype

The concept of the genotype is founded upon the conviction

that the directly observable phenomena of heredity can be rationally explained. Rational explanation means an adequate explanation in contradistinction to the fallacious or pseudo-explanation.

First of all, a correct explanation should consist of neither "petitio principii" fallacy nor a "regressus in infinitum." In more concrete terms:

a) the genotype's agency should not be conceived as something which reveals these properties of phenotype which constitute the "question-raising" element of genetic theory. If it were so, the whole explanatory value of the genotype would be illusionary, and another "super-genotype" should have been postulated.

b) The concept of the genotype should not be reduced to the random influences of the non-animate surroundings because, as we have seen, the phenotypic phenomena are not reducible to this kind of causality.

c) The genotype has to provide an answer to the questions concerning the repetitivity of the whole life cycle, not only a part of it. For, as we have seen (section 3.3), the life cycle constitutes the basic, empirical element of hereditary theories.

d) Finally, the genotype, according to the requirements of our contemporary monist ideology, has to be conceived as a physical body constituted from the matter present in the in organic surroundings. The term "reality," according to the monistic doctrine, should not be legitimately used for the entities which are not composed of elementary particles, atoms or molecules. Everything which is real, objective, has to be finally reducible to these entitative elements, or to the forces and interactions observed between them. In this sense, the concept of the genotype should be ultimately reducible to the inorganic matter.

These are the basic premises which determine the speculative framework in which the idea of the genotype was born and developed. Let us analyze it now in its details, and let us see how successful it is.

6.S The distinction between the active aspect of the genotype and the entitative aspect of the genotype

At the beginning of our analysis, we heave to distinguish between the idea of genotype as an *"agency"* and the idea of the genotype as an *"entity"*. By introducing this distinction we do not want to exclude a priori that the genotype may be, for example, a sort of "pure act," or to insist, to the contrary, that it is ontologically heterogeneous. What we do want to stress is the simple fact that for more than fifty years the genotype was conceived exclusively as an agent, while its entitative properties have belonged to the domain of sheer guesses, without any speculative (rational) or empirical (experimental) confirmation. At the same time this distinction will help us to discover the deeper level of metaphysical convictions which are operating within the apparently positivistic structure of biological speculations.

The distinction between the "active" properties of the hereditary material and its "entitative" aspect is quite obvious today (see, e.g., Baer et al., 1971/240), and in this sense modern genetic theories constitute a striking case of continuity between the old Aristotelian ideas and the results, of recent speculative effort.

6.4 The genotype as an agent

> "The genotype may be likened to the machinery that makes modern automobiles -- the automobiles representing the phenotype -- with the environment furnishing the necessary raw materials" (Herskowitz, 1973/339).

The existence of an already finished car has not to be supported by any special, separate being. The car exists on its own. But its *genesis* is explained in terms of the special agency, or rather, a set of agencies located in a factory. Delbrück has pointed out that the old Aristotelian ideas about the nature of the reproductive (hereditary) material are quite similar to the genetic modem ones.

> "The creature produced from them (the form principle in the semen and the matter coming from the female) is produced like a bed comes into being from the carpenter and the wood" (Aristotle, GA I, 21, 729b, 17-18).

Delbruck gives the following commentary, to the above text:

> "The form principle is likened to a carpenter. The carpenter is a moving force which changes the substrate but the moving force is not materially contained in the finished product" (1971/54).

The same important thought, which underlies the distinction between the phenotype and genotype, was stated by Woodger in the following manner:

> "The objects with which the chemist and physicist deal are supposed to be composed of the atoms or other particles. … But the object of biological study...is not supposed to be composed of genes...The gene is designed [postulated - PL] to explain the distribution of the characters [which are *composed* of atoms or other particles -PL] among such a generation of whole organism. The genes are not composing units in an ordinary atomistic sense -- not even the cell is composed of genes …" (1967/ 366-7).

The meaning of all these texts seems to be clear enough. As the factory that makes automobiles should not be identified with the automobile itself (and its intrinsic complexity of structure is only "genetically" reducible to the process of its production), as a carpenter should not be confounded with the wood or with the bed already made, so the active principle responsible for the appearance of the heredity traits (whether considered separately or in their totality) should not be identified with those traits.

The above speculations on the nature of the activity of the genotype's agency may be easily translated into the notion of "constraints" (see Pattee, 1970/117; 1972/248-258). A "constraint" does not "enrich" the material upon which it acts. In fact, the material is capable of assuming a number of different forms, or of revealing a number of different dynamic states. A "constraint" simply limits this intrinsic potential of the material.

The *repetitive* epigenesis demands an explanation simply because no earlier step in an epigenetic path is intrinsically determined to the production of the later step (see sections 3.20 and 3.21). In a way, a constraint reduces the inherent potentiality of inorganic matter, of organic molecules, of cells within the organs...and so on. So the constraint adds nothing. And that is why, as in Aristotle's metaphor, no entitative element is added to the bed by the carpenter, in the same sense no part of the genotype is supposed to enter into the entitative element of the phenotype.

Still, the genotype, in a way, *acts* upon the phenotype. It is responsible for a trans-temporal sequence of limitations which produce a final relatively heterogeneous structure from the relatively homogeneous one (see section 3.21 on the concept of the increase in complexity). We may try now to summarize the above-described properties of the genotype in the form of the Postulate of Heterocatalysis.

6.5 The Postulate of the Heteroaatalytic potential of the genotype

The observational and theoretical background which underlies the Postulate seems to be this:

Ia	The life cycle as a whole constitute a case of truly epigenetic process	(The observational evidence which has disproved the preformationist theory)
Ib	The life cycle appears repetitively	(The observational evidence)
Ic	The repetitive epigenetic process postulates the existence of external "constraints"	(A metascientific generalization, based upon the physico-chemical laws, probabilistic calculations and a sort of a vague idea of the principle of causality)
Id	The random influences of inorganic surroundings of the life cycle cannot be considered as an adequate source of the above external constraints	(A complex reasoning dependent upon a vague metascientific idea of adequacy and upon the empirical evidence)
Ie	The earlier steps of the epigenetic process do not provide the source of the adequate constraints for the later ones	The notion of the epigenetic event [section 3.21])

So:

> An agency (the genotype, the genome, the hereditary material, the set of genes...etc.) is to be postulated, and it has to be conceived as a sort of "constraint" intrinsically irreducible either to the inanimate surroundings or to the phenotype's reality.

The most serious problem involved in the Heterocatalytic Postulate is the idea of trans-temporal causality (see sections 5.8 and 5.9). The directly observable epigenetic process is not reducible to the functional event. So it cannot be explained in terms of the intrinsic properties of a functional structure. The notion of the increase of complexity means that the later stages of the epigenetic process cannot be interpreted in terms of the determinations inherent in the earlier stages. At the same time, it would not help us very much if we were to split the single idea of the genotype controlling the whole life cycle into a series of separate "fragmentary genotypes" controlling, "constraining" the particular sequential supposedly a-temporal steps of the life cycle, or any of its developmental paths. We have to leave this problem open, for we are not in the position to solve it at this moment of our study. But it is necessary to see the problem clearly,

however far-reaching its theoretical consequences may be.

The repetitivity of the life cycle's phenomena does not only force us to recognize the need for a non-random genome's agency, but it constitutes "question-raising" evidence on its own and requires a proper, adequate explanation. This explanation is formulated in the form of the Postulate of Auto-catalysis which we are now going to discuss.

6. 6 The Postulate of the Autocatalytic potential of the genotype

The non-random repetitivity of the phenotypes puts forward not only the problem of *how* a single genome controls the development of a single pheno-typic trait, or a whole organism's life cycle, but also how the number of identical phenotypes might be explained without invoking a super-agency producing new genomes. If the repetitivity (reappearance) of the phenotypes cannot be explained in terms of random environmental influences, neither (a fortiori) could the multiplication of the genomes be explained in terms of the environmental influences alone. So the postulatory genome's agency splits its hypothetical power in two. One consists of the capacity to drive the whole "bunch" of the developmental pathways up to their final (adult, reproductive) stages. This power, as we already know, constitutes the essence of the Postulate of Heterocatalysis. Another consists in the capacity to copy itself and is commonly referred to as the *autocatalytic* activity or potentiality.

The two activities seem to be relatively independent not only conceptually but phenomenally. Upon the phenomenal level we may observe that an egg, for instance, may be developmentally active, but the originating adult and functional body does not necessarily have to be fertile. There are instances in which the production of the apparently normal eggs or early developmental stages goes on in a quantitatively impressive way but the successive developmental stages do not appear at all.[101]

Upon the conceptual level, we might possibly imagine such a substance which would be able to copy itself, without being at the same time

[101] Muller (1922) discussing the theory of random changes in the genotype (chance mutations) states:

> "the most remarkable feature of the situation is not ... autocatalytic action in itself -- it is the fact that, when the structure of the gene becomes changed, through some 'chance variation,' the catalytic property of the gene may become correspondingly changed, in such a way as to leave it still autocatalytic..." (quoted after Fruton, 1972/243).

Holtzer and his collaborators (1972/330) make a clear distinction between the "proliferative life cycle" which is responsible for increase of similar cells, and the "quantal" cell cycle during which a specific part of the genome's heterocatalytic potential becomes actualized.

capable of promoting the developmental sequence o£ events.

We may reconstruct the origin of the Autocatalytic Postulate in the following schematic way:

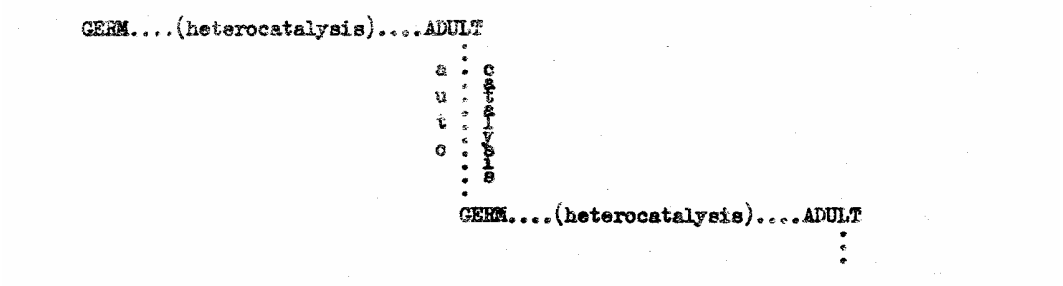
IIa	For a single life cycle at least one genotype is necessary	(the Heterocatalytic Postulate)
IIb	The coexistence of identical life cycles postulates the coexistence of the identical genotypes	(an inference from the empirical evidence and from IIa)
IIc	The preformation of genotypes is ruled out	(a theoretical premise of unclear origin)
IId	The inorganic, surroundings are not capable of producing the new genotypes	(an inference from the heterocatalytic postulate [see Id])
IIe	The genotype may copy itself directly, or indirectly, by the intermediate of its phenotype. In either case its origin is to be attributed to its own activity.	(an inference from the above)

So:

> The genotype is to be conceived as capable of copying itself (either directly or indirectly).

The second postulate of the genome seems to be in contrast with an ancient Aristotelian thesis which says that only an adult form (perfectly expressed upon the phenotypic level) is able to create the new copy of itself; that only this perfect form is capable of reproduction(see Aristotle GA, 734b, 34-6; Ritter, 1932/385).

The Aristotelian thesis might be schematically represented in the following way:

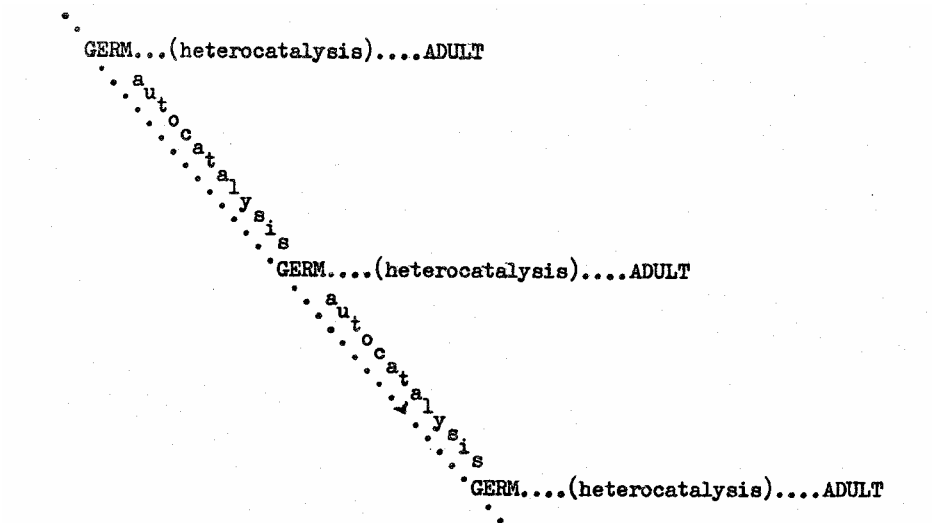


In this hypothesis the adult form constitutes a necessary intermediate stage conditioning the reproductive process.

Now, the Weismannian scheme (generally accepted up to now) puts the stress upon the autocatalytic self-sufficiency of the genomic agency.

> "The child inherits from the parent germ-cell not from the parent body...the body is, as it were, offshot from the germ cell" (Wilson, 1900, quoted after Moore, 1972/78).

This phrase might still be interpreted in the Aristotelian sense if the germ cells are conceived as the product of the *adult* phenotype. But modern genetics, and probably Weismann himself, interpreted it quite differently. The germ cells were supposed to be the *direct* product of the germ cells and the new (numerically different, but essentially identical) genotype was supposed to be derived *directly* from the genotype.[102] So the Weismannian scheme of the multiplication of the organisms would be this:



The heterocatalytic process observed upon the level of the phenotype may be identified with the so-called "life cycle" of a given organism, and of course, some more or less repetitive forms of "adaptive" phenotype have to be

included here too (sporulation, for instance, and so on).

In order to confirm the above presentation of two main postulates of the genotype (genome),

[102] Ritter referring to the modern ideas on the process of reproduction whites: "...the parent...does not after all really produce his own offspring, as in ordinary experience he seems to and as according to Aristotle's teaching he actually does" (1932/394). "...Weismann impose un changement de perspective: au lieu de voir dans 1'oeuf le chemin qui va d'un adulte à un autre adulte, nous verrons dans 1'adulte le chemin qui va d'un oeuf à un autre oeuf..." (Sentis, 1970/45).

we will have to look at some historical evidence concerning the development of the theory of the genome.

6. 7 Some historical evidence concerning the idea of heterocatalytic and autocatalytic potentiality of the hereditary material

Although the two main postulates of the genome were never stated in a formal way, we can easily trace them throughout the .whole history of modern genetic thought.

The Heterocatalytic Postulate's origin is obviously related to the collapse of the preformation theory. In 1900, E.B. Wilson writes:

> " How do the adult characteristics lie latent in the germ-cell; and how do they become patent as development proceeds?
> "...The gross errors of the early preformationists have been dispelled. We know that the germ-cell contains no predelineated embryo; that development is manifested, on the one hand, by the cleavage of the egg, on the other hand, by a process of differentiation, through which the products of cleavage gradually assume diverse forms and functions, and so accomplish a physiological division of labour...The real problem of development is the orderly sequence and correlation of these phenomena toward a typical result. We cannot escape the conclusion that this is the outcome of the organization of the germ-cells; but the nature of that which, for lack of a better term, we call 'organization,' is and doubtless long will remain almost wholly in the dark..." (quoted after Moore, 1972/79).

Almost a half century later, Muller (1947) characterizes the properties of the "genetic material" in this way:

> " … it is obvious that the whole congeries of variable processes of each kind of organism tends to go in a succession of great cycles, or generations — and that at the end of every cycle something very like the starting-point is reached again. Now the finding of the starting-point in a complex course, were it observed in any other field, would be taken to imply the existence of some guide or guides, some elements that...serve as a frame of reference in relation to which the passing phases of other features are adjusted..." (quoted after Moore, 1972/208).

E. Bell in 1966 summarizes the story in the following words:

> "Classical genetics has left us with the axiom that the morphological, functional and biochemical characteristics of an organism are dependent on its genetic constitution" (1966/229).

The Heterocatalytic Postulate of the genome concept is without doubt a causal idea. The term "cause" was used explicitly by Weismann and it is obviously

implied in such expressions as "guide," "information," "control," "determiner,"...and the like (see section 2.6).

But the heterocatalytic activity of the genome constitutes only a part of its inherent "power." The Autocatalytic Postulate attributes to it, as we have seen, a new and different role. It was clearly stated in the works of Weismann, for he thought that:

> "...a part of the specific germ-plasm [hereditary material, genome -PL] is not used up in the construction of the body of the offspring but is reserved unchanged for the formation of the germ-cells of the following generation..." (1885, quoted after Moore, 1972/59).

Apparently, Weismann considered the germ-plasm as a sort of building blocks from which the phenotype was eventually constructed. This suggestion was abandoned completely in the further development of genetic theory. But the above quotation implies the role of the germ-plasm in the formation of the new hereditary material. Muller, a half century later, states the Autocatalytic Postulate in this way:

> "In the organism — the return to the starting-point finds all structures doubled in a cell cycle,...And this...requires that the material furnishing the frame of reference, whatever it is, itself underwent such doubling or reproduction, and that this too must have taken place under its own guidance..." (1947).

And further on he clearly distinguishes the two postulatory activities of the genetic material:

> "...the essential process of reproduction consists in the autosynthesis of a controlling genetic material...The building up of the non-genetic [phenotypic -PL] parts of the system would then take place, conversely, by a series of essentially heterosynthetic processes, that were ultimately controlled by the genetic material..." (1947).[103]

The notion of the developmental event and its repetitivity might lead us to the formulation of a third postulate of the genome, namely, the postulate of its integrative nature (see section 5.8). The fact of the trans-spatial integration adds a new element to the traditional heterocatalytic postulate which was conceived rather as a sort of exclusively trans-temporal constraint. It is not clear, however, whether the notion of integration has to be conceived as the active or rather entitative property of the genotype's agency. For this reason we will leave this problem open, and we will return

[103] Levine (1971/2) writes: "Hereditary material must perform two functions: (1) it. must replicate itself and (2) it must provide for protein synthesis." Implicit in this statement is the opinion that given the proteins all the problem of epigenesis is solved. We will discuss the validity of this opinion in the next chapter of our study.

to it in the latter part of our study.

The two "causal" postulates of tie concept of the genetic material (genotype, genome) constitute only part of this concept. In fact, there are two other important ideas necessarily implied by it and we might call them the Postulate of Stability and the Postulate of Complexity.

6.8 The Postulate of Stability of the genotype

The recurrent character of the phenotypic traits being the most mysterious element of the directly observable life phenomena, its causal explanation had to postulate something relatively independent from the homogeneous or random environmental influences. So not only the self-copying (autocatalytic) potential of the genotype was postulated to be extremely precise and faithful, but its influence upon the phenotypic sphere (hetero-catalytic potential) was postulated to be always the same. In other words, the genome's causal influence (both auto- and heterocatalytic) had to be conceived as a *stable dynamic pattern.*

This stable dynamic pattern, however, must be carefully distinguished from the *stable* (repetitive) pattern of the phenotypic phenomena. The *identity* of phenotypes should not be confused with the *stability* of the genetic material. The identity of a concrete phenotype is a sort of *external* relation, while the *stability* of the genetic material constitutes its *intrinsic* property. The phenotype is intrinsically *unstable* (see section 3.15). It is different in every moment of its existence. Its overall form, its dynamics, change constantly during developmental, adaptive and functional processes on every organizational level of its reality. Its molecular, chemical composition is never the same. The atoms and small molecules are entering and leaving its sphere, so that between the phenotype and its surroundings a constant flow of matter may be registered.

The genetic material has, theoretically, to be completely different. If it were to undergo such, or at least analogous, transformations as the phenotype does, the explanatory value of the concept would be null, for it would provoke a new and essentially the same theoretical problem as the phenotype did.

The detailed structure of the Postulate of the Stability of the genome may thus be represented as follows:

IIIa	External influences affect at least the dynamic properties of bodies	(An explanation of the concept of “influence”)

IIIb	The phenotype is influenced by the environmental dynamics	(Observational evidence)
IIIc	The phenotype reveals a nonrandom repetitivity both in its entitative and dynamic aspects	(Observational evidence)
IIId	The repetitivity postulates the existence of the genome	(The Heterocatalytic Postulate)

So:

> In contrast to the phenotype, the genome is relatively (at least) immune in its dynamics from the environmental influences.

The postulate of the stability of the genome's agency has had a profound impact upon the early evolutionary ideas. Weismann, who stated the essentials of the postulate in an explicit way, was quite conscious of this fact:

> "In my opinion — the substance of the germ-cells transfers its hereditary tendencies [potentiality -PL] from generation to generation. . .always uninfluenced in any corresponding manner, by that which happens during the life of the individual which bears it. If these views be correct, all our ideas upon the transformation of species require thorough modification, for the whole principle of evolution by means of exercise...as professed by Lamarck, and accepted in some cases by Darwin, entirely collapses" (1883, quoted after Wilson, 1900).

It is clear that if the genetic material were completely stable, completely immune from environmental influences, it would not only constitute a sort of exceptional entity in the physical sense. Its stability would prevent once for ever any really essential change in the properties of the phenotype it produces. It was only after the discovery of mutation that the idea of the absolute immutability of the genetic material was undermined and a new theoretical (at least) chance of the transformation of a species has appeared again. But it must be stressed here that the dichotomy between the "anti-burglary" character of the genotype's entity and the more vulnerable phenotypic aspect of an organism automatically cleaved all the environmental influences into two separate categories.[104] One sort of environmental influence produces the *irrversible* changes,

[104] "The above may be illustrated by Mailer's statement: "...no relation was observable between the environmental or physiological condition of an organism and the kind of effect produced by the gene mutations that might arise in it..." (1947).

and the other one produced the *reversible* ones. Any change which affects the entitative aspect of the genetic material should, in principle, lead to a new repetitive pattern of phenotypic phenomena. This pattern might be modified again and again if (against the Postulate of Stability) the entitative aspect of the genetic material were subjected to environmental influences. But the reversal to the original state is (theoretically) extremely improbable because of the Postulate of the Complexity of the genome which we will discuss in the next section. The idea expressed in the Postulate of Stability of the genotype may be illustrated by innumerable examples taken from the contemporary molecular genetics. Holtzer et al (1972/251-2), for instance, postulates that because a "definitive stem cell" must last the life time of the organism in order to provide the new differentiating lineages of the cells, this stem fs "time independent." Time as such being deprived of any causal potentiality, the idea of "time independence" amounts 'to the idea of independence from the environmental influences. Holtzer and his collaborators add that it "must be a system of molecules whose stability is independent of time." Yates et al (1972/112), discussing the recent date on the repair of DNA molecule, point out that this evidence diminishes the validity of the previously widespread opinion about the invariance of DNA molecule, and they explicitly state that beyond the "invariance" of DNA lies "another system of invariances." (See also Pallade 1965/181).
The Postulate of Stability of the genotype is certainly one of the basic elements of the whole concept of the hereditary material. It has had an immense influence upon the interpretation of the biochemical data concerning the identity of the genetic material, but the true limits of its stability and the empirical criteria of tracing the eventual modifications of it are still not clear enough.

6.9 The Postulate of the Complexity of the genetic material

The problem of complexity of the genome seems to be primarily an epistemological one. Would it be rationally satisfying to attribute an evidently complex effect to an entitatively simple agent? What are the epis-temologically sound criteria to recognize within the set of many agents this one which provides the adequate explanation of the observed effect? More concretely we might ask, for instance, what sort of rational process has led to the recognition that the moon and its motion around the earth provides the main element in the process of the causal explanation of tidal phenomena.

Turning back to our problem of the adequate explanation of the extremely complex phenotypic phenomena,we are facing this dilemma: granting that the complexity of the phenotypic phenomena postulates an adequately complex activity of the genetic material, would it be right to attribute such a complex activity to an entitatively simple being?

The obvious complexity of life phenomena manifested by a cell provoked, for instance, in the nineteenth century some cautious remarks on the apparent homogeneity of the cell membrane, cell protoplasm and cell nucleus. Brücke wrote in 1861:

> "We cannot imagine a living, growing cell with a homogenous nucleus and a homogenous membrane, and which contains a simple solution of albumen, since we do not find in this protein those phenomena which we call the life process. We must therefore ascribe to the living cells, besides the molecular structure of its constituent organic compounds, a more complex structure of another order, which we call organization" (quoted after Fruton, 1972/488).

This refusal to accept the apparently "empirical" evidence has been found to be completely justified in the light of the recent electron microscope studies which have led to the new outlook upon the structural and dynamic properties of submicroscopic cellular phenomena and have finally overcome the previous theories based upon the assumption of the relatively random dynamics and homogeneous structure of fundamental cellular processes.

Basically the same way of thinking has led to the Postulate of Complexity of the genome, which was stated by Weismann in the following way:

> "...I have assumed that the ["germ plasm"] possesses a highly complex structure, conferring upon it the power of developing into a complex organism..." (1885, quoted after Moore, 1972/59).

The Postulate of Complexity of this genetic material is stated here quite explicitly. Its more detailed conceptual structure might be represented in this way:

IVa	The hereditary phenotype represents a spatially and temporally complex phenomenon	(the observational evidence)
IVb	The complexity of the phenotypic phenomena has to be matched by the adequately complex influence of the genetic material	(the Postulate of Heterocatalytic activity of the genome, the concept of adequacy between the influence and its effect)

IVc	A complex activity implies an adequately complex entitative aspect of the agent	(a sort of metaphysical and/ or epistemological axiom)

So: The genetic material is entitatively complex.

The above postulate had a decisive impact upon the interpretation of the chemical data concerning the structure of germ cells and their nuclei in particular. The phosphorus containing acid material present in the nuclei of cells was already discovered by Miesher in 1871. But its chemical structure seemed to be so desperately homogeneous (as compared with the extreme complexity of the phenotypic protein compounds) that for about eighty years it was constantly rejected as a possible candidate for the role of the genetic material.[105] It was only Dunce's (1952) and Gamow's (1954) hypothesis that the sequence of nucleic acids in the molecules of Miesher's compound (known today as DNA) might determine the aminoacid sequence in the protein polypep-tides, which has made it possible to reconsider the role of the DNA in the hereditary processes. But of course, the Dunce and Gamow hypotheses (further developed by Watson and Crick) have completely reversed the analytical trend in biochemistry, introducing back again the necessity of avoiding both the homogenization, the randomization of biological structures, on the one hand, and the too far-reaching separation of the biological structures, on the other.

The Postulate of Complexity raises some rather difficult problems not only upon the observational level but on the speculative level, too.

First of all, it is difficult to trace the origins and evaluate the strength of the axiom IVc. Complexity as such tells us nothing about the actual dynamic properties of an entity. Something may be extremely complex and at the same time lacking in capacity to influence its surroundings. One might then say that the complexity is a sort of necessary but not sufficient property of the genotype agency. But is the complexity a really necessary attribute of the somewhat mysterious constraints we are looking for? These constraints are supposed to exert a trans-temporal and a trans-spatial control over the epigenetic. process.[106] How should this complexity be conceived?

Could a static structure of great complexity exert a trans-spatial and a trans-temporal control? If the structure were not static, what about the Postulate of Stability? Are we not trapped in a vicious circle of "petitio principii" fallacy?

The nature of the heterocatalytic activity of the genome was for a considerable period

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[105] "...The principal obstacle in considering nucleic acids as possible 'auto-synthetic molecules' was the apparent uniformity and simplicity of their chemical structure..." (Fruton, 1972/245).

[106] In the context of the sex reversal phenomena Chan writes: "as every trait must have its genetic background and the adult phenotype the result of a series of developmental steps, a structure should not be defined as the form at a single stage of the life-history. Rather it should be represented by the whole sequence of forms that make up the ontogeny; more accurately, it should not be defined only as the forms but rather as the sequence of the series of changes that underlie the change of forms. It would seem that the determination of sex, i.e., organogenesis of the gonad and subsequent events concerning the maturation of the germ-cells, is governed by a system of multiple factors of relative male and female tendency, which in whole, controls the sequential events in gonadal ontogeny and its physiological function throughout the life-history" (1970/67-8, Italics - PL).

of time conceived in terms of an enzymatic model (see Fruton, 1972/241). This analogy, however, is radically false. An enzyme acts in essentially the same way for a practically unlimited time. The genotype, on the contrary, has to be conceived as something which acts differently in each succeeding step of the epigenetic process. How reconcile the Postulate of the Stability of the genotype with the Postulate of its Heterocatalytic potential?

The stability stressed by the third postulate cannot be conceived in terms of activity. That is obvious. The only reasonable solution in sight would mean an intrinsic split between the entitative and the active aspect of the genotype's reality. But this conceptual cleavage does not help us really very much. We are back again with the idea of an "unmoved mover." The complexity of the entitative aspect of the genotype would be then a sort, of quite redundant postulate. We have to leave all these problems unanswered. We wanted, however, to put them clearly in order to show the intrinsic complications of the idea of genotypic agency.

Before we start discussing the fifth Postulate of the genotype, namely, the postulate of its Chemical nature, we have to reflect upon the relationships which exist between the preformation ideas and the content of the four previously discussed postulates of the concept of the genome.

6.10 The concept of the genetic material and the preformation idea

As we have seen before, the theory of preformation was discarded because

of the accumulation of the empirical evidence concerning the reality of epigenetic phenomena upon every organizational level of the phenotypic reality. The introduction of the concept of the genome was a sort of compromise between the extreme preformationist opinion and the extreme epigenetic opinion.

The Postulate of Heterocatalytic activity of the genome re-introduces within the sphere of the living organism something which reduces the puzzling "de novo" element of the epigenesis. Because of this postulate the phenotype's epigenesis is based on something *preformed.* The"formative" agency of the genome is transmitted from one generation to another in a *preformed* state. The Postulate of Complexity of the genome, in fact, mitigates or even reduces completely the apparent developmental change within the life cycle. The idea of the genome which carries all the information expressed gradually, step by step, during the epigenetic processes has replaced the problem of the "de novo" creation with the problem of *translation.* The phenotype is conceived now as a physically equivalent counterpart of the genome. The process of heterocatalysis means the change from one form of complexity into another one. Like a pendulum which swings from one extreme position to another one, both being physically equivalent, so the heterocatalysis is sometimes conceived as a change from one form of structural and dynamic state into another one. A strict physical reducibility of one state to another would make the concept of epigenesis meaningless. Epigenesis still remains valid as a sort of observational phenomenon, but its reformulation in terms of the effect of the heterocata-lytic activity of the genotype removes the causal problem which might have been seen there before.

The postulate of the Autocatalytic capacity of the genotype further mitigates the problem of the epigenesis. It attributes to the genotype's reality something which was previously refused to the phenotypic reality, namely, the capacity of self-copying. So the genotype becomes the weariless source of new copies of new genotypes and of new phenotypes as well.

But the price which was paid in order to obtain such a solution of the intriguing problem of epigenetic phenomena is rather high. The whole concept of the organism is split into two elements which to a certain extent manifest physically different properties. The phenotype is changing continuously, its entitative structure and functional dynamics appear gradually upon ever new organizational levels. The genotype, to the contrary,

remains stable. As Delbruck rightly pointed out, the genotype behaves as an "unmoved mover" (1971/55).

But the monistic doctrine requires that both realities be conceived as a chemical entity or a chemical process. This requirement constitutes the fifth postulate of the genome, namely, the Postulate of its Chemical Nature.

6.11 The problem of the chemical structure of the genome

The opinion which postulates that what is supposed to exist is necessarily composed of atoms which constitute the parts of the mineral world is generally known as materialistic monism. According to this doctrine, atoms differ one from another not because their parts are different but because they are differently arranged. Similarly the chemical molecules, crystals, living organisms (including man) are differing not because their parts are different. They are all composed from atoms, but the arrangement of those atoms is different. The reconstruction of a proper arrangement of atoms yields the desired chemical molecule, the right crystal, the right protein molecule, or a right living body. In the future the right protein molecules (and some other chemical molecules properly arranged) will yield the first artificially produced but living cell...and perhaps the first artificial (but let us hope completely normal) man.

> " — after millenia of illusions, doubts and probing, it turns out that...unique properties [of living systems] are due to the way in which common chemical elements are put together in time and space. For our times, life -- human life included --is an outcome of an elaborate organization based on trivial ingredients and ordinary forces..." (Pallade, 1965/179).

That is the predominant opinion in modern biology, especially in molecular biology, and the idea of the genome is of course not excluded from this all-embracing view.

It might be interesting to detect the historical transformation of the Aristotelian idea of "soul" (vegetative, at least) into the idea of "hereditary material" and later on into the idea of the genotype. Hall (1969, II, 326) very aptly describes the main theoretical elements which have led Haeckel towards materialistic monism. It started with the desire to eliminate an apparently unnecessary "super-natural," "divine" element in the normal course of events, and has led to. the negation of the intrinsic "natural" dualism which was characteristic (according to the Aristotelian tradition) to the living bodies (see also Rensch, 1971/335). At the same time the more or less

gratuitous thesis of "continuity" of real entities has led monists to more or less explicit negation of any essential differences between the apparently different beings. The reality of the distinction between such categories as the "substance" and the "accident" being discredited even earlier, the monistic idea of the "unity of the Universe" entered without any serious difficulty into the basic set of scientific (or rather "meta-sci-entific") assumptions of modern science. Weismann quite spontaneously accepted this monistic idea during his attempt to elaborate the vague concept of the "hereditary material" postulated by Spencer and Nageli.

> "...The determining and directing factor is simply and solely the nuclear substance, the nucleoplasm, which possesses such a molecular structure in the germ-cell that all succeeding stages of its molecular structure in future nuclei must necessarily arise from it, as soon as the requisite external conditions are present. This is almost the same conception of ontogenetic development as that which has been held by embryologists who have not accepted the doctrine of evolution,[107] for we have only to transfer the primary cause of development, from an unknown within the organism, into the nuclear substance, in order to make the views identical" (quot. by Moore, 1972, 66).

We may believe that Weismann actually was convinced about the identity of the two views, but it does not necessarily mean that he was right. For the Aristotelian idea of soul (the determining and directing factor of the developmental events) is not an easy concept, and unfortunately, it is usually treated as a sort of Cartesian, vitalistic idea. The Aristotelian concept of soul (vegetative one) presupposes the earlier understanding and acceptance of the difference between the substance and accidents, the understanding of his theory of the "active potential" and the "passive potential," his theory of "form" and "matter," and more generally his theory of change (see Siwek, 1965/30-38). All this is too complex to be explained here. The Cartesian vitalistic idea of soul, more recently put forward (upon the level of a sheer speculation) in the form of Maxwell's demon (see Johnson, 1965; Daub, 1970) was (perhaps because of its simplicity) replacing completely the original Aristotelian concept of "soul." Weismann "extracted" the invisible Cartesian gnome from an "unknown source within the organism" and inserted it in the equally unknown "chemical substance." On -the level of the "localization" no difference could be traced between tte Weismannian and the Aristotelian

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[107] The expression seems to be a sort of a polite euphemism for the term "vitalists," or "vitalistic doctrine."

doctrine of the "hereditary material," for Aristotle evidently never doubted that his "soul" is present in every developmental stage, including the egg. On the level of its "power," the Weissmannian and the Aristotelian ideas as quite alike too. The main difference is most paradoxical. The Weismannian "complex chemical molecule" endowed in its special power is extrinsic to the rest of the organism, and it remains always separated from it. The Aristotelian soul is not-separable, in principle, from the matter of the given body. We will not enter into discussion of the possible advantages or disadvantages of the Aristotelian concept of "soul" (the vegetative one).[108] What we wanted to stress was this. Weismann was the first who reduced the "hereditary material" to the purely chemical material, without discarding or limiting the range of the hereditary problem itself. He saw clearly what the "hereditary material" has to do, and at the same time he was courageous enough to be consistent with the monistic ideology of materialism.

The theoretical and empirical background of the Postulate of the Chemical nature of the genotype may be represented in the following way:

Va	The autocatalytic and the heterocatalytic properties are inconceivable without an adequate entitative background. A "pure" activity does not make sense.	(A meta-scientific generalization)
Vb	The stability of the genotype makes it irreducible to the phenotypic element of the life cycle	(The Postulate of Stability)
Vc	Any real entity has to be conceived as composed of atoms	(The monistic axiom)

So:

The genotype's agency has to be conceived as a sort of chemical structure.

The Postulate of Chemical Nature of the genotype constitutes the most important idea of modern molecular genetics. We cannot trace all the

[108] On Aristotle's contribution to embryology see Needham, 1959/54.

history of experimental and speculative efforts which were finally crowned by the theory which identifies the genotype with the giant molecule of de-oxy-ribonucleic acid (DNA). In the next chapter we will be trying to verify to what extent the three first and basic postulates of the genotype are reconcilable with the empirical evidence concerning the role of DNA molecule in the processes of life.

Before we pass to the critical evaluation of the contemporary theories concerning the entitative nature of the genotype's agency, we should discuss for a while the experimental evidence which gives us a sort of hint about some details of the "active" properties of the genotype. This evidence is usually represented by such abstract concepts as "totipotentiality," "pluripotentiality," "determination" and the like. These concepts are of crucial importance for the right understanding of the nature of the role of the genotype in the organism, and for this reason we will have to reflect upon their meaning.

6.12 On the evidence concerning some intrinsic properties of the genotypic agency

The concept of "totipotentiality" summarizes the vast empirical evidence which demonstrates the practical indivisibility of the genotype's agency. In fact, it was shown that the full heterocatalytic potential is not confined to the germ cell, but it may be traced in virtually any, more or less differentiated, cell of the adult or the developing phenotype (Spemann, 1914/216-221; King and Briggs, 1956/271-90; Steward et al., 1958/693-703; 1958a/705-8; Steward and H. Y. Mohan Rama, 1961/189-265 ; Pasternak, 1970/ 133). Not only the unicellular organisms transfer the whole, undivided heterocatalytic potential to their progeny, but practically every cell in the multicellular structure of an adult form of a plant or of a metazoan body contains the same heterocatalytic (and autocatalytic) potential as the germ cell (Gurdon, 1962/127-47; 1966/95-9; Hildebrandt, 1970/147-67).[109]

The influences which may reveal this unexpected potentiality are relatively complex, but still completely inadequate to explain the origin of this potentiality. We have to admit that a non-random set of environmental sequential influences is necessary to release this "totipotentiality"

[109] This rather strange fact was registered or perhaps guessed as early as 1902 by Haberlandt. He expressly stated the possibility of producing embryos from cell cultures (see Hildebrandt, 1970/158).

of a functional, differentiated cell, but at the same time we cannot claim that this non-random set of influences has produced this "totipotentiality" "de novo."

In other words, every single cell, whether bacterial cell or a metazoan cell, or a plant cell, seems to contain the whole undivided genotype.[110] Consequently, the number of the genotypes in a single multicellu-lar body equals the number of cells in this body.[111]

The process of differentiation consists in the partial expression of this "totipotentiality." The muscle cell expresses one "part" of its "whole" genotype, the neural cell another "part" of the essentially same, but numerically different genotype, the bone, the cartilage or the glandular cell still another "part" of the whole genotype. But it is possible to separate such a differentiated cell fromthe whole context of its "life cycle" and by a proper experimental procedure "force" it to develop in a complete "life cycle." In this way the cell's full genotypic potentiality ("totipotentiality") may be demonstrated.

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[110] This general statement should not mean that it is easy to change any cell of a multicellular adult body into a new complete one. "The cell has to be exposed to a succession of specific stimuli applied in a definite sequence" (Schjeide § De Vellis, 1970/11). The identity of these specific stimuli and the proper timetable of the process is known only in a few cases. Some times the conversion of a differentiated cell into a whole life cycle seems to be completely impossible. In these instances "The most likely explanation...for inability of adult nuclei to substitute completely for the egg nucleus, probably is the difficulty of quickly erasing the consequences of differentiation of the chromosomes in the transplanted nucleus" [Markert and Ursprung, 1971/135). Of course, the above statement makes reference to the King and Brigg's technique of revealing the whole genotypic potential of a cell. The nucleus transplanation does not constitute the unique empirical proof of "totipotentiality" of somatic cells.

[111] Schwann has postulated the totipotentiality of cells in the multicellular organisms already in 1847. " — all organized bodies are composed of essentially similar parts, namely, of cells;...these cells are formed and grow in accordance with the essentially similar laws; and, therefore,...these processes must, in every instance, be produced by the same powers. Now, if we find that some of these elementary parts, not differing from the others, are capable of separating themselves from the organism, and pursuing an independent growth, we may thence conclude that each of the other elementary parts, each cell, is already possessed of power to take up fresh molecules and grow; and that, therefore, every elementary part possesses a power of its own, an independent life, by means of which it would be enabled to develop itself independently, if the relations which it bore to external parts were but similar to those in which it stands in the organism...The failure of growth in the case of any particular cell, when separated from an organized body, is as slight an objection to this theory, as it is an objection against the independent vitality of a bee, that it cannot continue long in existence after being separated from its swarm..." (quoted after Baker and Allen, 1970/51; see also Wightman, 1951/389ff.).

Another important concept abstracted from the empirical observations upon the nature of genotype's activity is the concept of "determination" (see Holtzer et al., 1972/230). It was shown that apparently homogeneous cells (the cells which are identical observationally) may nevertheless differ one from another in this developmental potential which will appear in each one of them later on. The fact of determination does not contradict their virtual "totipotentiality." It means only that in spite of their actual phenotypic identity, and in spite of their basic genotypic identity ("totipotentiality") they may exist in an intermediate state of "partial" disposition, which may be transmitted from one generation to another, without being expressed upon the phenotypic level,[112] and without loss of the full "totipotentiality."

This "determination" may be univocal (towards a single, particular form of phenotypic partial expression) or more ambiguous (towards a certain more or less limited range of partial phenotypic expressions). In the last case the word "pluripotentiality" is conmonly used. The states of "determination" and "pluripotentiality" may, however, revert to the "totipotentiality" but the change from one particular form of determination into another form (of direction) of determination ("transdetermination") is also possible.[113] (See Markert, 1963/65-84; Braun, 1969/134ff.; Nozeran et al., 1971/1-66; Garrod & Ashworth, 1973/407).

In a concrete case a cell which has reached the full phenotypic expression of its particular determination (a muscle cell, for instance) may gradually lose its phenotypic particular functional characters, it may "dedif-ferentiate" to the state of an apparently "primitive" stage and start again the process of development reaching eventually a completely new, different but

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[112] Sentis commenting on the phenomena of determination writes:

"Les charactères latents deviennent des propriétés mystérieuses, qui se cachent au sein des êtres vivants et font résurgence au bout de plusieurs générations" (1970/ 38).

[113] Perhaps the most spectacular known example of transdetermination is the so-called Wolffian lens regeneration observed in amphibia. - After the surgical extirpation of developed lens in an amphibian embryo, it regenerates from cells of the ridge of the iris (see Spemann, 1967/78ff.; Wolsky and Wolsky, 1968; Goss, 1969/197-206; Hamburgh, 1971/67-69; on nerve regeneration see Sperry, 1965/ 39).

equally functional state of phenotypic maturity (the state of a chondrocyte, of an osteocyte ... etc. See, e.g., Waddington, 1962/3-5; Goss, 1969; Willmer, 1970/52, 57).

The complexity of the empirical evidence upon which the above generalizations are based prevent us from entering into a detailed discussion of these facts. But one things has to be stressed at this point. The concepts of "totipotentiality," "pluripotentiality," or "determination" constitute a sort of speculative elaboration of the empirical evidence, and they all belong to the sphere of an abstract, postulatory idea of the genotype. They seem to be relatively independent from the validity of such theoretical ideas as the Postulate of the Complexity of the Postulate of the Chemical Nature of the genotype. They do, however, affect, the right understanding of the Postulate of Heterocatalysis,[114] the Postulate of Autocatalysis and the Postulate of Stability of the genotype's agency.

The notion of "determination" reveals the obvious functional "organization" within the heterocatalytic potentiality of the genotype. The "determination" in fact is always closely related to a particular, concrete functional phenotypic expression. The "determination" cannot be described in terms of homogeneous, continuous, intrinsically divisible spatio-temporal coordinates. Its concrete meaning is always intrinsically heterogeneous and obviously linked with the concept of the functional structure.

Parallel to the "quantic" nature of functional events and developmental events, the concept of "determination" is "quantic," too. Berill, describing the process of gradual formation of various cellular elements of blood (erythropoiesis), writes:

> "...In the bone marrow an undifferentiated stem cell receives a stimulus which directs it toward the erythrocytic series. This may be called 'determination,' for it is an all-or-none phenomenon..." (1971/480).

Of course, the "determination" is not directly observed. What is observed is its further phenotypic expression. Here we should make a clear distinction between the concept of "determination" and the concept of heterocatalysis. Both concepts belong to the level of interpretation of phenotypic

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[114] Hood and Prahl write:

> "The genome of each vertebrate cell may contain all the library of information that is required to construct a new organism (Gurdon and Woodland, 1970). Yet, in the differentiated individual cell, only a minuscule subset of this information is expressed" (1971/203).

If the total genome is present in every cell, however differentiated it may be, what constitutes the actual constraining element of the concrete phenotypic form?

directly observable data. But they refer to the different aspects of this evidence. In order to understand it better, let us imagine a child's toy, an electric train which runs round the maze of the rails. On the switchboard there are many buttons which determine the way the train will go through the maze. But the construction of the track relaying system (including its remote control, signalization and so on) does not explain the machinery of the engine which pulls the carriages along a given track. How to apply this metaphor to the distinction between the heterocatalytic potential of the genotype and the concept of "determination" within a genotype? The epigenetic origin of different functional structures in the body postulates a different framework of genotypic constraints for each particular developmental path. A given form of differentiation postulates a specific nature of constraints. These constraints might be compared to the engine which makes the carriages of the train progress along a given track. The process of determination on the other hand might be compared to the process of selection between the different tracks, and being analogous to the track relaying system does not explain the epigenetic nature of a given developmental phenomenon, but refers to the selection of a given "part" of genotypic constraints.[115]

The hereditary character of "determination" reflects upon the meaning of the Postulate of Autocatalysis. A determined cell may multiply, its genotype may be copied a number of times without any loss of particular "determination" (see Hadorn, 1968/192-199).

Finally, the stability of the genotypic agency has to be conceived not as a univocal condition, but rather as a hierarchy of different levels of stability. The most basic level of stability is reflected by the idea of the essential "totipotentiality" of every cell, however restricted its phenotypic expression might be.

The next level of stability is represented by the idea of "pluripotentiality." The essentially "totipotential" cells may divide and multiply being actually restricted in their "totipotentiality" and still not being determined to any particular functional phenotypic expression. The third level

[115] The virtual lack of a clear distinction between the concept of the heterocatalysis, and the concept of the determination leads to a tremendous ambiguity and lack of precision in the evaluation of the "question-raising" evidence and the formulation of the essential problem of epigenetic phenomena (see, e.g., Jacobson, 1966/25).

of stability is represented by the state of "determination."[116] The particular "determination" may be shown to be stable for a number of generations of cells, without being expressed upon the phenotypic level (Holtzer, 1970/ 77; Nöthinger, 1972/1-34).

6.13 Some general conclusions on the nature of genotype's concept

As we have seen, the concept of the genotype represents a complex idea to which different empirical and theoretical elements are contributing. Every postulate makes recourse to some meta-scientific generalizations, extrapolations or even to obviously metaphysic beliefs. The postulates do not seem to be reducible one to another. It is not clear to what extent each one of them is really necessary for the proper explanation of "question-raising" evidence observed upon the phenotypic level of the life. The first three postulates seem to constitute an inevitable set of explanatory speculative devices. However, these three postulates tell us nothing about the entita-tive aspect of the genome. The other two postulates are obviously affected by monistic metaphysics. The Postulate of Complexity and the Postulate of Chemical Nature of the genotype might possibly need a more careful study before their validity will be ultimately vindicated. But we do not think it proper to do it now. We will rather try to investigate how the above five postulates meet together in the theory which identifies the genotype with DNA molecule.

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[116] "...Differentiation is not adequately described in terms of the activation of individual [Mendelian -PL] genes: it entails the activation of integrated genetic patterns...Differential utilization of the genome presupposes a choice between multiple integrated genetic patterns available for use as effective genomes. The available choices constitute the facultative genome" (Foulds, 1969/360). In the above text Foulds distinguishes between the total genome (corresponding to the idea of "totipotentiality"), facultative genome (corresponding to the idea of "pluripotentiality") and the effective genome (corresponding to the idea of "determination"). "Developmental potentiality of a cell lineage can now be equated with what Abercrombie (1967) proposes to call the epigenotype, i.e., with that portion of the genome which, under appropriate conditions, can be expressed, while the rest of it remains silent. This implies...two different phenomena:
"1) determination, the process which selects a particular segment of the genome which thereafter will be expressible (but not necessarily expressed in a given cell lineage) to the exclusion of the others,
"2) differentiation i.e., the process which results in the actual expression of the selected segment..." (Ephrussi, 1970/20).

CHAPTER SEVEN

THE DNA DOUBLE HELIX MOLECULE AND THE ACTIVE PROPERTIES OF THE GENOME'S AGENCY

7.1 The origins of the theory which identifies the genome with the DNA molecule

Stent (1970), in an extremely clear way, summarizes the epistem-ological problems involved in the identification of the genotype's agency with a concrete material entity. He recognizes that the concept of genotype as developed by classical genetics constitutes a kind of "indivisible and abstract unit" and he stresses its "transcendental" properties.

> "So far as [the term] 'transcendental' is concerned, I have now eliminated it, as a possible source of confusion, even though I still think that its common (rather than Kantian) meaning, namely possessing attributes so fantastic as to be beyond ordinary comprehension, is applicable to the classical gene" (quoted after Moore 1972/252).

Further on Stent formulates a basic question we want to discuss in this chapter:

> "...how could one recognize a gene as a gene even if one happened to lay eyes on it?..." (ibid./253)[117]

Being aware of the fact that the genetic material (the genotype, the genome) has been identified with the double helix of DNA macromolecule we may paraphrase Stent's question. How could one be sure that on looking at the DNA molecule one is dealing with the genotype?

The development of the theory which identifies the genome with the giant molecule of DNA is extremely complex. The Postulate of Stability has led to the obvious implication that the genome is "localized" within the nucleus of the germ cell (see Hughes, 1959/82; Stubbe, 1972/187, 252). The microscopic analysis has revealed that the male sperm consists of the locomo-tory devices and the nucleus alone, in some species, and that during the fertilization the nucleus alone penetrates the ovum, while all the other parts of the sperm remain outside. So if the offspring shows the traits of its male parent, the nucleus of the sperm constitutes the only entitative link

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[117] "...There is nothing like looking, if you want to find something (or so Thorin said to the young dwarves). You certainly usually find something, if you look, but it is not always quite the something you were after. So it proved on this occasion..." J.R.R. Tolkien, *The Hobbit or There and Back Again.*

between them. This of course does not necessarily imply that the same is right in the case of the ovum. But the idea that both parents in an equal measure participate in the formation of the offspring was (and still is, in a sense) deeply rooted in the mind of biologists, so that the idea about the nuclear localization of the genome was accepted unanimously against the rather misogynist opinion of Aristotle and his followers. Now, the nucleus of the living cell is (from the chemical point of view) composed almost exclusively of proteins, histones and deoxyribonucleic acids.

> "For nearly 30 years... it was assumed more or less implicitly that the specificity of the gene resided in the protein part of nucleoprotein" (Whitehouse, 1970/167).

Nucleic acids were thought to be too simple in their chemical structure, and so they were ruled out on the basis of the requirements put by the Postulate of the Complexity of the genome. The same might be said about histones (Markert and Ursprung, 1971/90). In 1944 it was definitively shown that DNA is influencing the phenotypic transformation of some bacterial forms (Avery et al., 1944). This, of course, suggested that to the DNA a heterocatalytic role might be attributed (See the Postulate of Heterocatalysis). Later on it was shown that the various specimens of the same species, the various tissues and the various cells of the same specimen have essentially the same DNA content (see Loomis, 1970/1). This (at least superficially) seemed to fit the requirements of the Postulate of the genome's Stability. Finally, almost at the same time, in the fifties, both the Postulate of the Autocatalytic Potential and the Postulate of the Complexity were found to apply (within certain limits) to the DNA molecule. The discovery of the code-like structure of DNA has revealed its true complexity, hidden under the rather unimpressive "surface" of only four nucleotide bases sequence (Sturtevant, 1965/104 ff.).

In the previous chapter we have analyzed the details of the concept of the genotype. We know that its autocatalytic and heterocatalytic potential constitutes, together with its stability, a sort of indivisible set of properties. If an entity is unstable, it cannot pretend to fulfill the requirements implied in the concept of the genotype. If an entity cannot copy itself, it cannot seriously be considered as a candidate for the role the genotype is expected to play. Finally, if an entity is fpund to be incapable of providing an adequate set of constraints for the organism's developmental processes,this entity does not stand up to the-requirements put forward for the genotypes' agency, it cannot perform the task the genotype is supposed to fulfill during the organism's life cycle.

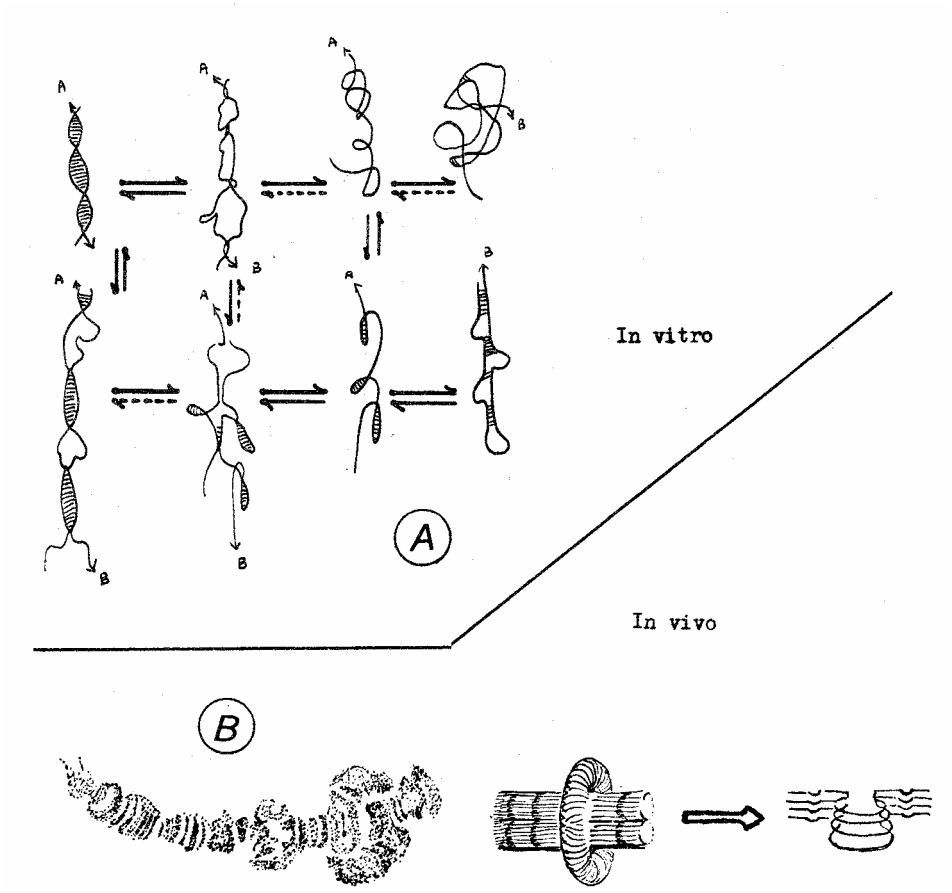

Fig. 7.1 Different structural states of the DNA molecule.
A - Reversible transformations of the DNA double helix molecule provoked by random environmental influences. (After Mahler & Cordes 1966)
B - The reversible non-random chromosomal "puff" which is observed at a specific developmental stage of Chironomus tentans.
Diagrams below illustrate the details of the "puff" and the way in which the chromosomal DNA is locally uncoiled for transcription into mRNA. (After Gardner 1972)

In this chapter we will not try to evaluate critically the evidence which has led to the identification of the genotype with the DNA molecule. This evidence one may find in such detailed monographs as for instance White-house's (1971), Florkin's(1971) and Fruton's (1972). We will limit ourselves to the analysis of this evidence which concerns directly the already known mechanisms of DNA replication and translation. We will try to see to what extent they do represent a case of true "self-replication" and true "hetero-catalysis."

7.2 The DNA and the process of its replication

The autocatalytic potential of DNA was suggested for the first time by Watson and Crick in the following terms:

> "...A genetic material must in some way fulfil two functions. It must duplicate itself, and it must exert a highly specific influence on the cell. Our model for DNA suggests a simple mechanism for the first process, but at the moment we cannot see how it carries out the second one...' (1953).

In order to understand better the relationship between the exact meaning of the term "auto-catalysis" as understood in the context of genetic theory, and its use in Watson and Crick's model, we have to discuss some essential details of the latter.

Watson and Crick have proved that in the living organism the DNA molecule exists in the form of an extremely long "zip-fastener" in the "closed" state. The cotton band of a zip-fastener may represent the phosphate backbone of the desoxyribonucleic polymer, while single tiny metal pieces, which like teeth are projecting from each of the two parts of the zip-fastener (in the "open" position) may help us to imagine the position of nucleotides in each of the two complementary chains of the DNA helix. While in the zip-fastener each metal piece is like the other, in the DNA molecule there are four different forms of nucleotides, namely, the adenine (A), thymine (T), cytosine (C) and guanine (G). In the zip-fastener each metal part of one strip "fits" to any of the metal parts of the second strip. In the DNA molecule the fitting may be observed only between A and T, or C and G. While in the zip-fastener in the "closed" position, both strips are held together by mechanical forces, in the case of the double helix the two chains are held by hydrogen bonds formed respectively between the A-T and C-G pairs. Finally, the zip-fastener either in the "closed" or "open" position may be straight or folded in various ways while in the case of the double DNA chain in the "closed" position, the molecule

is twisted spirally round its longest axis (see Fig. 7.1).

After these preliminary explanations we may pass to the discussion of the process of the "auto-replication."

The process of the so-called "self-replication may be divided into three different phases:

A. The phase of the separation of two complementary nucleotide chains (see Fig. 7.2A);

B. The phase of the attachment of the free bases to their "favorite" partners (adenine to thymine, cytosine to guanine, guanine to cytosine and thymine to adenine)(see Fig. 7.2B);

C. The phase of tying up the neighboring free bases attached to the "maternal chain" (see Fig. 7.2C).

During the first phase, the hydrogen bonds between the paired deoxy-ribonucleotides are broken down, so that the whole line of polynucleotide is free to tie up the single nucleotides present in the medium. In this way the newly-produced double helix will be composed of a single "old" strand (or chain) and the "new" one arranged according to the pattern of the "old" one. This model of replication is called "semiconservative."

The problem of separation of chains is extremely complicated and unsolved, so far (Fruton, 1972/253-4). We will stress only one point, the length of the cell's DNA molecule as compared with the diameter of the cell itself (see Fig. 5.4). The DNA molecule is by several orders of magnitude longer than the cell, and we have to remember that (1) the random linkage between the separated chains (see Fig. 7.1) would interfere with the process of replication, and (2) that the process of replication is effected, in vivo, in less than half an hour.

During the second phase, the single nucleotides are attached to their "partners" along the "open" helix. The pool of the nucleotides is strictly regulated. During each cell cycle only are the nucleotides produced "de no-vo," but even the enzymatic machinery needed for their production apparently is built up "de novo" each time and then destroyed (see Braun, 1969/36; Thrasher, 1971/181; Ord and Stocken, 1973/170). We also have to remember that the process of replication is similar to the process of transcription (see Section 7.8), but in the latter case a completely different pool of nucleotides happens to be available. This of course occurs repetitively, and it postulates a precise spatial control of an extremely large number of heterogeneous molecules.

During the third phase, a special enzyme polymerizes free nucleotides attached to their respective chains of the "old" DNA half-molecule. A simple

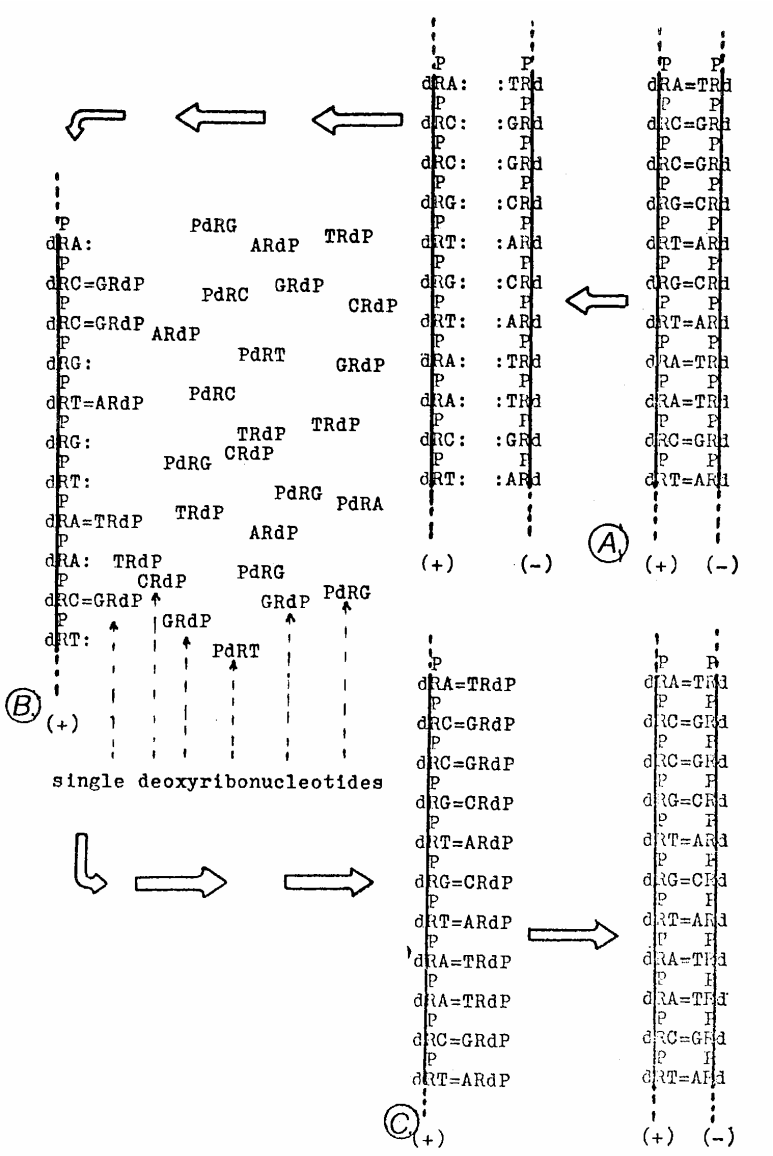

Fig. 7.2 Three main phases of the DNA molecule replication process.

A - Separation of the (+) strand from the (-) strand.

B - Single deoxyribonucleotides form hydrogen bonds (=) with deoxyribonucleotidee constituting (+) strand. The esentially identical replication of the (-) strand is not represented on the scheme.

C - Newly attached bases are polymerized bv a specific enzyme.

procaryotic chromosome being composed of some 3,000,000 nucleotide pairs could not be replicated during twenty minutes by a single enzyme molecule. The recent evidence suggests that the chromosomes might be replicated in segments and subsequently linked together again by a specific polynucleotide ligase (see Herskowitz, 1973/48-9). The non-random

utilization of energy which is necessary for the replicative process constitutes a problem on its own.

7.3 The DNA and the Postulate of Autocatalysis

In the light of the above facts, we have to conclude that the process of the so-called "auto-" or "self-replication of DNA cannot be physically explained by the intrinsic properties of the DNA helix alone. The helix as such has no physically evident capacity to divide (to "open") itself, to collect in its environment free nucleotide bases of specific structure, nor to bind them (polymerize) together once they are attached in the proper place. The only specific function of the separated, single chain halves of the DNA helix consists in preferential pairing of the adenine by thymine and *vice versa*, or the guanine by cytosine and *vice versa.*

When Watson and Crick state that:

> "...the specificity of DNA self replication is accomplished without recourse to specific protein synthesis and that each of our complementary DNA chains serves as a template or mould for the formation onto itself of a new companion chain..." (1953/18),

it might mean that the authors are taking the separation of double helix into single chains for granted, that they take the production of new free (non-polymerized) nucleotide bases for granted and that they are taking the consequent polymerization of specifically arranged free nucleotides for granted.[118] But, of course, the authors are aware of these problems. In the same paper they are discussing theoretical difficulties involved in the problem of separation of chains. The difficulties are rather serious. In 1966 Cairns wrote that the separation of circular helix DNA molecule strands in some bacteria capable of replicating it in about twenty minutes would postulate the

[118] There is no doubt that the terminology is misleading. Beadle, for instance, writes: "...the Watson-Crick structure [the model of DNA double strain molecule] immediately suggested how it replicates or copies itself with each cell generation, how it is used in development and function, and how it undergoes the mutational changes that are the basis of organic evolution" (Beadle, 1969/2). None of these problems is really understood up to today, and what is understood applies to *in vitro* models which do not justify such an overstatement as quoted above (see also Schaffner, 1969/339).

spinning of the molecule with the velocity of 15,000 revolutions per minute.[119]

The polymerization of phosphate "backbone" presents another problem to be solved. It *is*, of course, "solved" by the living cell, but the explanation of its physical nature postulates the non-random and highly effective enzymatic activity of a specific protein molecule or even a whole set of molecules.

Summing up, we may say that the new copies of DNA helix are appearing "de novo" as a result of a highly complex and non-random set of events in which quite a number of different chemical compounds is participating. The replication of DNA molecules represents an example of physical process which goes on on the condition that some structural elements are coexistent, non-randomly localized in space, that the adequate amount of energy is released in the right place and at the right time. The structural elements taking part in this process do not exist in. the inorganic surroundings of bacteria, so that their *"de novo"* formation is to be postulated.[120]

The *intrinsic* properties of DNA molecule *do* explain why the newly-formed copies of it are strictly identical but not *why* they are formed at all. The repetitive, non-random process of DNA replication reveals essentially the same properties as any other functional event does. And the repetitivity of this process postulates an appropriate developmental system as in the case of any other phenotypic functional repetitive event.

In other words, the replication of DNA observed in the living bodies is neither structurally nor dynamically reducible to the DNA molecule alone.

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[119] 0n hypothetical models of DNA replication see Herskowitz (1973/45ff.). We should carefully distinguish in our mind two quite different levels of scientific interpretation. One level consists in stating an inevitable, necessary postulate. If one faces the empirical fact of DNA non-random multiplication, he must admit that an appropriate (non-random) mechanism for its multiplication does exist. In this sense the postulatory "mechanism for DNA multiplication" should not be confused with a "model for DNA multiplication" which refers to a specific, hypothetical detailed concept about how this mechanism actually works. The term "model" should not be used in reference to the first concept which is already firm and irrevocable: a mechanism exists. In many respects the process of DNA replication, is ultimately known, in the same sense in which since Harvey many aspects of blood circulation are ultimately known. However, both in the case of blood circulation and in the case of DNA replication some details remain unknown, and to them the term "model" should be applied.

[120] In 1973 Donachie and his co-workers wrote: "The genome of E. coli [one of the most intensively studied procaryotic organisms] consists of a single closed circle of DNA. This circle, about 1200 milimicrons in circumference, has been the object of intensive study, both genetical and biochemical. Nevertheless, probably no more than 10% has so far been identified with specific genetic functions (see Taylor, 1970) and the biochemical mechanism of its replication is still not understood (see Gross, 1972, for review). Even less is known about the spatial and temporal organization of this enormous molecule within a cell which is itself only about 2 microns in length" (1973/10). "DNA— [contrary to widespread opinion] is not a self-replicating molecule ...At least two different enzymes are required...ATP must be added...Thus it is the living system, not any one of its molecules, which is self-replicating— the nucleotide bases and sugar groups must be synthesised from smaller molecules...These syntheses are catalysed by a battery of enzymes, each one of which must be assembled on the basis of information provided by its own particular enzyme...two additional phosphate groups should be added --phosphorylating enzyme needed...DNA replication...therefore [is] different in many respects from the simple growth of an inorganic crystal..." (Stebbins, 1972/81ff.).

A far greater and non-randomly organized system has to be postulated, and the necessity of specific "constraints" which would explain the integration of developmental events which lead to their origin is as obvious here as it was in the case of other life cycle's phenomena. Only an abstract treatment of the facts, un unwarranted elimination of physically necessary elements of the whole process might create a mental illusion of "self-sufficiency" of the DNA molecule. The DNA replication thus presents a new "question-raising" evidence rather than the "question-solving" one.

7.4 Proteins and the Postulate of Heteroeatalysis

The full meaning of the postulated heterocatalytic potential of the genome cannot be understood without the recognition of the functional properties of the heterogeneous chemical molecules appearing de novo during the developmental life cycle of living organisms. At the moment, however, we will try only to sketch the most essential problems raised by protein synthesis alone.

Let us reflect upon a concrete example, and the conclusions we will draw from it will be generalized upon a broader spectrum of the biochemical events.

One of the main functions of blood is to transport the oxygen molecules from the lungs to the intercellular fluid of other tissues and organs. The erythrocytes (red blood cells) contain a special substance which in a sense "attracts" the randomly wandering oxygen molecules dissolved in the blood plasm circulating round the pulmonary alveoli, transports them and

Alpha chain		Beta chain		Alpha chain		Beta chain		Alpha chain		Beta chain	
1	Val	1	Val	5o	His	5o	Thr	95	Pro	1oo	Pro
	¦	2	His	51	Gly	51	Pro	96	Val	1o1	Glu
2	Leu	3	Leu	52	Ser	52	Asp	97	Asp	1o2	Asn
3	Ser	4	Thr	53	Ala	53	Ala	98	Phe	1o3	Phe
4	Pro	5	Pro		¦	54	Val	99	Lys	1o4	Arg
5	Ala	6	Glu		¦	55	Met	1oo	Leu	1o5	Leu
6	Asp	7	Glu		¦	56	Gly	1o1	Leu	1o6	Leu
7	Lys	8	Lys		¦	57	Asn	1o2	Ser	1o7	Gly
8	Thr	9	Ser		¦	58	Pro	1o3	His	1o8	Asn
9	Asn	1o	Ala	54	Gln	59	Lys	1o4	Cys	1o9	Val
1o	Val	11	Val	55	Val	6o	Val	1o5	Leu	11o	Leu
11	Lys	12	Thr	56	Lys	61	Lys	1o6	Leu	111	Val
12	Ala	13	Ala	57	Gly	62	Ala	1o7	Val	112	Cys
13	Ala	14	Leu	58	His	63	His	1o8	Thr	113	Val
14	Try	15	Try	59	Gly	64	Gly	1o9	Leu	114	Leu
15	Gly	16	Gly	6o	Lys	65	Lys	11o	Ala	115	Ala
16	Lys	17	Lys	61	Lys	66	Lys	111	Ala	116	His
17	Val	18	Val	62	Val	67	Val	112	His	117	His
18	Gly	19	Asn	63	Ala	68	Leu	113	Leu	118	Phe
19	Ala		¦	64	Asp	69	Gly	114	Pro	119	Gly
2o	His		¦	65	Ala	7o	Ala	115	Ala	12o	Lys
21	Ala	2o	Val	66	Leu	71	Phe	116	Glu	121	Glu
22	Gly	21	Asp	67	Thr	72	Ser	117	Phe	122	Phe
23	Glu	22	Glu	68	Asn	73	Asp	118	Thr	123	Thr
24	Tyr	23	Val	69	Ala	74	Gly	119	Pro	124	Pro
25	Gly	24	Gly	7o	Val	75	Leu	12o	Ala	125	Pro
26	Ala	25	Gly	71	Ala	76	Ala	121	Val	126	Val
27	Glu	26	Glu	72	His	77	His	122	His	127	Gln
28	Ala	27	Ala	73	Val	78	Leu	123	Ala	128	Ala
29	Leu	28	Leu	74	Asp	79	Asp	124	Ser	129	Ala
3o	Glu	29	Gly	75	Asp	8o	Asn	125	Leu	13o	Tyr
31	Arg	3o	Arg	76	Met	81	Leu	126	Asp	131	Gln
32	Met	31	Leu	77	Pro	82	Lys	127	Lys	132	Lys
33	Phe	32	Leu	78	Asn	83	Gly	128	Phe	133	Val
34	Leu	33	Val	79	Ala	84	Thr	129	Leu	134	Val
35	Ser	34	Val	8o	Leu	85	Phe	13o	Ala	135	Ala
36	Phe	35	Tyr	81	Ser	86	Ala	131	Ser	136	Gly
37	Pro	36	Pro	82	Ala	87	Thr	132	Val	137	Val
38	Thr	37	Try	83	Leu	88	Leu	133	Ser	138	Ala
39	Thr	38	Thr	84	Ser	89	Ser	134	Thr	139	Asp
4o	Lys	39	Gln	85	Asp	9o	Glu	135	Val	14o	Ala
41	Thr	4o	Arg	86	Leu	91	Leu	136	Leu	141	Leu
42	Tyr	41	Phe	87	His	92	His	137	Thr	142	Ala
43	Phe	42	Phe	88	Ala	93	Cys	138	Ser	143	His
44	Pro	43	Glu	89	His	94	Asp	139	Lys	144	Lys
45	His	44	Ser	9o	Lys	95	Lys	14o	Tyr	145	Tyr
46	Phe	45	Phe	91	Leu	96	Leu	141	Arg	146	His
	¦	46	Gly	92	Arg	97	His				
47	Asp	47	Asp	93	Val	98	Val				
48	Leu	48	Leu	94	Asp	99	Asp				
49	Ser	49	Ser								

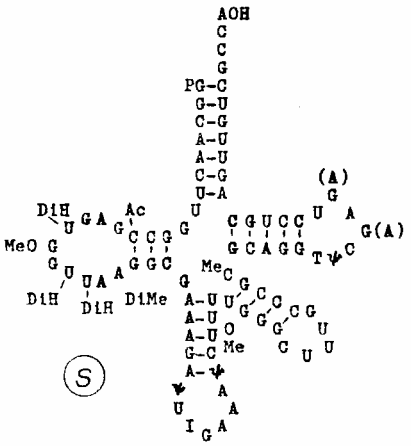
Fig. 7.3 The linear sequence of aminoacids in α- and β-polypeptide chains constituting a part of the human hemoglobin molecule.

releases them in the slightly different environment of other organs (the differences of pH, differences of the $C0_2$ concentration,of the O_2 concentration ...and so on). This substance is called hemoglobin, has a red color and belongs to the group of the chemical compounds called *proteins.* Its intrinsic structure is extremely complex. Twenty different amino acids (smaller organic molecules, each one composed of about 100 atoms of C, H, 0, N, S in different proportion and different spatial arrangement) are linked together in a very regular way (polypeptide bond) forming four long chains (the so-called polypeptides). Hemoglobin molecule is composed of two identical pairs of polypeptide chains (see Fig. 7.3), each pair in turn being composed of one α-chain (composed of 141 aminoacid residues) and one β-chain (146 residues). (See Perutz, 1964; Kendrew, 1969). In the very center of the folded α- and β-chains four iron atoms are attached to a complex structure of heme molecule. Putting all together a single hemoglobin molecule has 64,500 times the weight of a hydrogen atom and is made up of about 10,000 atoms of hydrogen, carbon, nitrogen, oxygen and sulphur, plus four atoms of iron. The four polypeptide chains contain a total of 574 aminoacid units. What is the function of this so complex organic compound?

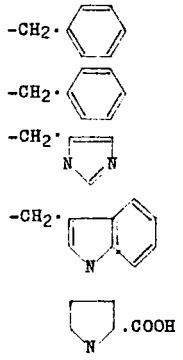
> "In the absence of an oxygen carrier a liter of arterial blood at body temperature could dissolve and transport no more than three mililiters of oxygen. The presence of hemoglobin increases this quantity 70 times...Similarly, hemoglobin is responsible for carrying more than 90% of the carbon dioxide transported by venous blood" (Perutz, 1964/39-40).

One cubic millimeter of blood contains over 5 million red blood cells, and each one of them contains about 280 million molecules of hemoglobin. (Ibid., 39). In the normal, non-pathological conditions despite their extreme complexity, they are *absolutely identical.*[121] We will leave out the problem as to how the four heme molecules are synthetized. We will limit ourselves to the following question. What sort of mechanism preserves the utmost

[121] In the case of such a big molecule as hemoglobin, the antigenic properties are to be expected, and this *a priori* implies that the copies of Hb molecules characteristic for a given life cycle will be to a certain extent different from equally normal (functional) molecules of other concrete life cycles. Stamatoyannopoulos reports that out of 68 variants of alpha chain Hb, 58 were found to be functionally and clinically benign (1972/53). This, it seems, might be interpreted in terms of an "individualizing phenotype" rather than a sub-normal, but clinically benign condition.



(R)adicals	Names Common abbreviations in brackets
-H	(Gly)cine
$-CH_3$	(Ala)nine
$-CH_2OH$	(Ser)ine
$-CHOH \cdot CH_3$	(Thr)eonine
$-CH_2 \cdot SH$	(Cys)teine
$-(CH_2)_2 \cdot SCH_3$	(Met)hionine
$-CH(CH_3)_2$	(Val)ine
$-CH_2 \cdot CH(CH_3)_2$	(Leu)ucine
$-CH(CH_3)CH_2 \cdot CH_3$	(Is)o(le)ucine
$-CH_2 \cdot COOH$	(Asp)partic acid
$-CH_2 \cdot CO \cdot NH_2$	(As)paragi(n)e
$-(CH_2)_2 \cdot COOH$	(Glu)tamic acid
$-(CH_2)_2 \cdot CO \cdot NH_2$	(Gl)utami(n)e
$-(CH_2)_3 \cdot NH \cdot C(NH)NH_2$	(Arg)inine
$-(CH_2)_4 \cdot NH_2$	(Lys)ine



(Phe)nylalanine

(Tyr)osine

(His)tidine

(Try)ptophan

(Pro)line

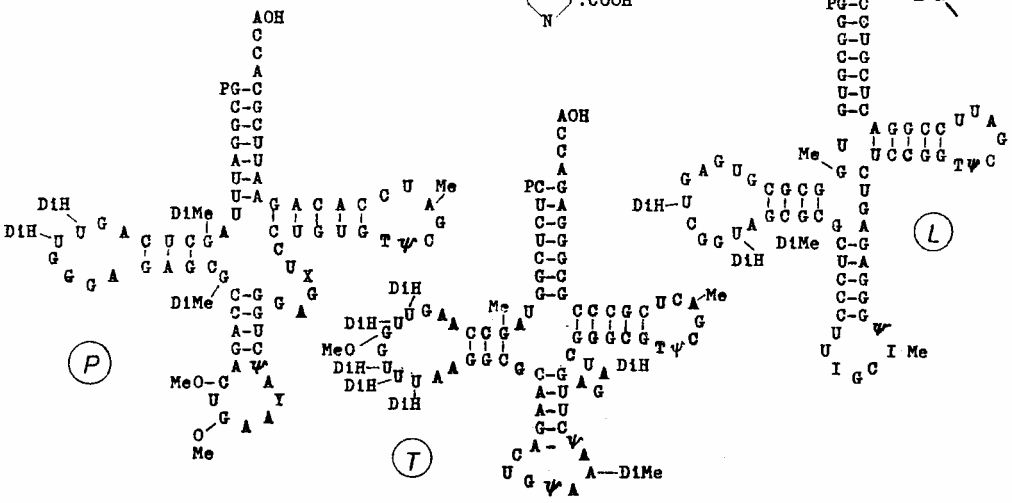


Fig. 7.4 Structure of aminoacids, polypeptides
and some of tRNAs (transfer RNAs).
A. - The characteristic groups (radicals) of 20 most common aminoacids.
B. - The general formula of polypeptides.
C. - Serine tRNA (from yeasts).
P. - Yeasts' phenylalanine tRNA.
T. - " tyrosine tRNA
L. - " alanine tRNA
(A, B after Whitehouse 1971, p. 213, fig. 13.2;
S, P, T, L after Herskowitz 1973, p. 32, fig. 3-10)

precision (repetitivity) of the hemoglobin production in different (numerically) bone marrow cells during the whole span of an individual's life?[122] The basic, essential details of this process are already known, and the DNA code plays an important role in this process. Yet the difference between an "important role" and the "main role" is almost as crucial as the distinction between the "indispensable element" and the "sufficient element." What is the role of DNA in the production of a functional protein (the hemoglobin, for example)?

> "...Proteins are essential building blocks of membranes, which maintain the physical integrity of organisms, and are also enzymes which catalyze metabolic reactions. Although the structure and metabolic activities of a cell are organized for its preservation, the protein components are continually being destroyed and replaced throughout the cell's existence. Therefore, an organism must possess initially, and must retain during its existence, instructions for producing proteins of correct kinds and amounts and at the correct times and places. Such information must also be transmitted to and maintained in its offspring" (Herskowitz, 1973/2).

Such functional molecules as, for instance, hemoglobin molecule are built from simpler organic elements (aminoacid units) which are continuously produced *"de novo"* by an extremely precise and efficient system of specific enzyme molecules. In this way the problem of the origin of a given functional molecule (e.g., myosin molecule, lens crystalline molecule, a digestive enzyme's molecule) depends upon a system of enzymes which produce the aminoacids, sugars and other "medium-size" organic molecules. In fact, practically every synthetic step observed in vivo is dependent upon a highly organized system of enzymatic structures.[123]

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[122] Fruton (1972/175) describes how in 1958 it was realized that the normal hemoglobin molecule (hemoglobin A) and the hemoglobin S molecule found in human subjects suffering from sickle-cell anemia differ because of the substitution of single glutamic acid unit by single valine acid unit in beta-polypeptide chains of the whole complex.

[123] "...peculiar advantages of enzymic catalysis [consist in its]...specificity ...and speed] in contradistinction to the *in vitro* chemical reactions]...in an enzymic reaction one mode of reaction is hastened but the others [side-reactions] are not. Side-reactions are thus avoided; instead of several ways over the hill there is one tunnel through it...Enzymic. reactions may proceed a thousand million times as rapidly as their non-enzymic counterparts. The difference corresponds, on a time scale, to the difference between seconds and centuries...the reactions in cells *[in vivo]* are organized in time. This is expressed metaphorically in the term 'metabolic pathway' [see Fig. 7.5). The pathway is a spatial concept but the term refers to temporal organization... There are a dozen successive reactions in the [glycolytic] pathway and each reaction is catalyzed by a separate enzyme. If one enzyme were missing, the corresponding reaction would not proceed at anywhere near an adequate rate, and so the whole pathway would be inoperative" (Waley, 1969/141-2).

We encounter here the empirical elements which determine the meaning of a developmental "all-or-none" event, and the meaning of trans-spatial and trans-temporal constraints (see sections 5.8 and 5.9).

7.5 Specificity of enzyme molecules and the Postulate of Heteroaatalysis

The heterocatalytic function of the genotype is sometimes conceived in terms of "constraints" which are sufficient to determine a unique, functional sequence of aminoacids in an enzyme molecule. What does it mean? It means that the functionality of biochemical synthetic (developmental) processes which are going on in vivo was discovered to be conditioned by the specific structural properties of some protein molcules. If we represented a concrete case of chemical reaction, a synthesis, or a lysis, by the metaphor of locking or unlocking a padlock, the enzyme molecule might be likened to a key which enables us to close or open the given padlock with the minimum expenditure of energy. Specificity of a biochemical reaction is determined by the structure of the interacting molecules. To create (or break) a link between two concrete molecules A and B a different molecular "key" is necessary and a different one in the case of the molecules B and C. Taking into account the enormous variety of functional structure of the living body, and the even more impressive number of their "precursors," we may imagine how many different enzymatic "keys" are necessary to create the proper, functional conditions for the developmental processes which lead to their formation, or decomposition.

As in the case of the padlock and key, their coexistence is a necessary but not sufficient condition for the act of opening or closing the door, in the same sense the coexistence of enzymes and their substrates is not a sufficient condition for the actual reaction between them. They have to be present in the proper place and at the proper time.[124]

[124] "The specificity of enzymes can be compared to the pins coming out of a radio tube which have different thicknesses and different spacing so that they fit into the socket only in one position -- that one which is functional...In principle, a number of pins which are indistinguishable would serve equally well except for the time it takes to try out and find the right position on the socket" (Gaffron, 1957/137). Note the time factor which may serve as a criterion for the evaluation of random and non-random models of enzymatic function.

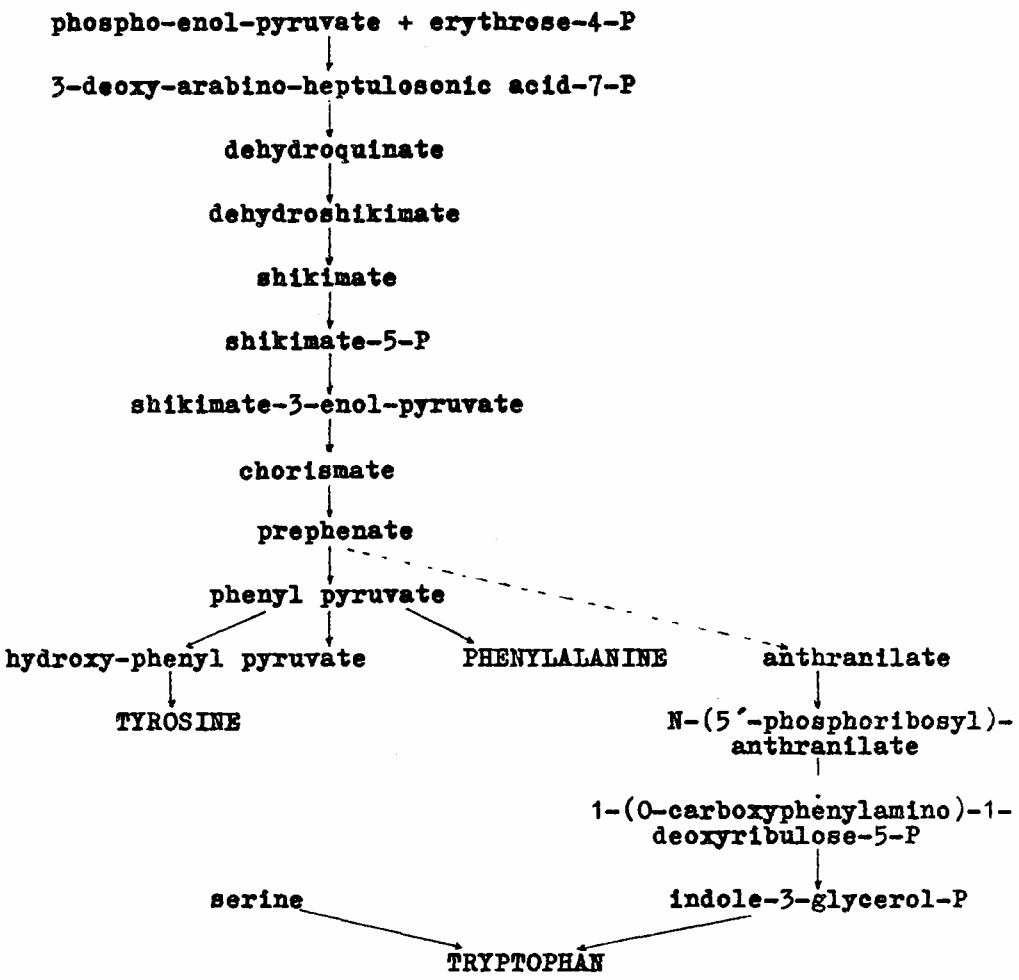

Fig. 7.5 A part of the biosynthetic pathway of three different aminoacids (tyrosine, phenylalanine and tryptophan). Both phospho-enol-pyruvate and eiythrose-4-P are the result of a complex' biosynthetic processes.

The enzymes involved in the successive stages of the pathway, the moments in which the energy has to be supplied, and the specific environmental conditions which determine the functionality of the energy transfer are not mentioned in the scheme. (After Hawker 4 Linton 1972, fig. 2.2)

For the sake of clarity, let us leave for the moment the problem of the constraints which determine the right spatio-temporal framework in which an enzyme molecule is expected to operate. Let us concentrate upon the process which leads to the "de novo" appearance of the enzyme molecule itself.

As in the case of any other functional structure, the problem of structural fit is crucial. That inevitably poses the problem of integrated epigenesis of many heterogeneous structures. At the same time, we should remember that the enzyme molecules, apart from being functionally efficient, are usually marked by an "individualizing" hereditary property which makes them characteritistic for a given species- or even for a concrete single organism.[125] And we should not forget that each concrete reaction in the body requires quite a number of identical enzyme molecules. In other words, three distinct problems are involved in the epigenetic origin of the biochemical machinery of living cells.

First, its structural elements have to fit one to another. This fit is necessarily postulated by the ultimate functionality of the system. This in turn creates the problem of the constraints which would properly integrate the necessarily separate processes of the production of the functional elements.

Secondly, any macromolecular part of the above machinery is observed to be "individualized" by a hereditary, although only intrinsically repetitive, structural trait. This postulates' the adequate constraints which would control the epigenetic appearance of this trait.

Finally, the quantity of structural elements has to be controlled. Each functional unit, in fact, is composed of the strictly determined number of parts which sometimes are alike, sometimes are different, but in every case

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[125] We should distinguish between the functional specificity of an enzyme (which is dependent upon the structural properties of the substrates and the nature of the reaction the enzyme has to facilitate),and the "individualizing" specificity of the enzyme which makes it characteristic for a given species or a given individual life cycle.

Both forms of specificity have to be conceived in terms of a unique aminoacid sequence and a unique folding of the protein molecule which makes the essential part of the enzyme. Mirsky and Pauling's definition of denatured protein ("The denatured protein molecule we consider to be characterized by the absence of a uniquely defined configuration," 1936/442-443) should not be interpreted in the sense that the "uniquely defined confirmation" means functional configuration.

they do appear in a non-random quantity.

Hundreds and thousands of unique enzymes are observed to appear *"do novo"* in the growing and differentiating organism. Each division of cells presupposes their multiplication. How then are they produced in the repetitive, precise way? What constitutes an adequate constraint for this extremely complex epigenetic process? At least five different elements determine the functionality of an enzymatic reaction:

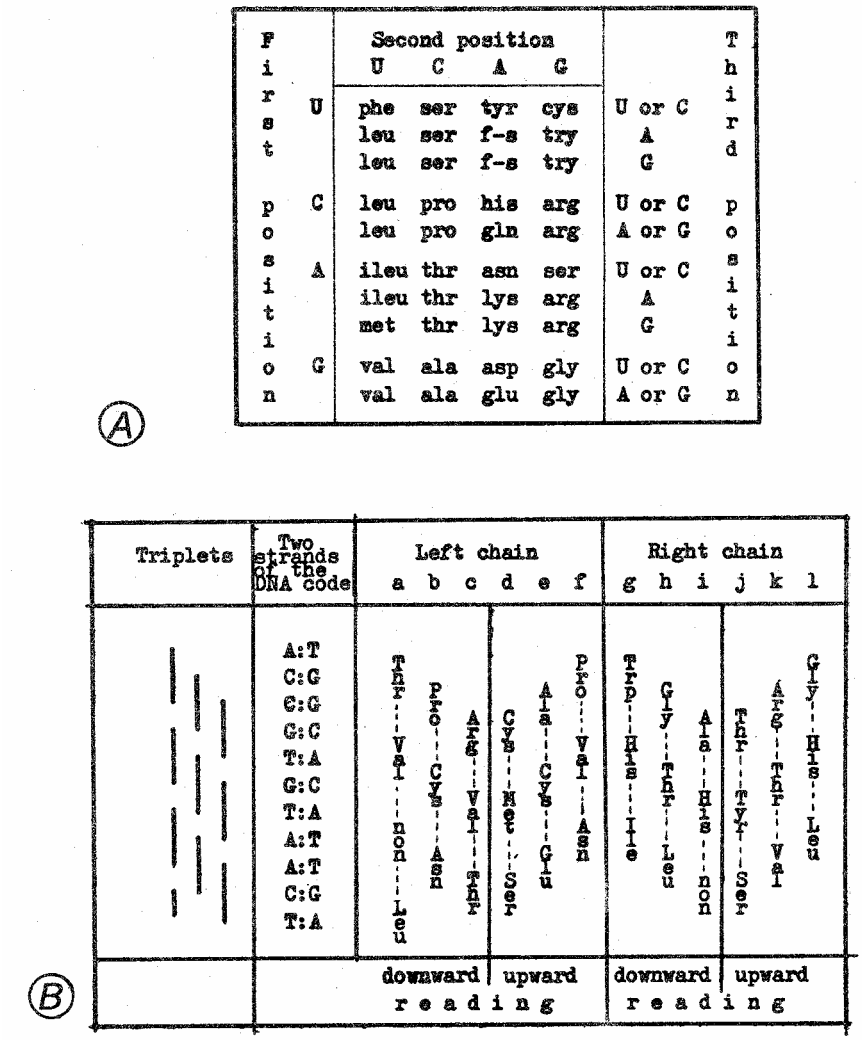
1) The structural fit between the enzyme and its substrates;
2) The antigenic properties of the enzyme;
3) The quantity of enzyme molecules;
4) The spatial arrangement of the interacting molecules, and possibly the whole spatial context of the preceding and following enzymatic reactions;
5) Availability of an energy source;
6) Other environmental parameters, such as temperature, pH, the concentration of ions, presence of non-protein groups and the like.

All these conditions are "synchronic," although their origin is "diachronic."[126] The genome's agency has to provide the answer for the "dia-chronic" developmental, epigenetic process which explains how the "synchronic" state of functionality is attained.
Now we will try to analyze to what extent the DNA. molecule contributes to this developmental process.

7.6 DNA molecule as a code for aminoacid sequence in functional polypeptides

The information for the production of the correct protein is at present believed to be encoded in the DNA helix molecule, and the process of the decoding of this information (or this information as such) is sometimes identified with the heterocatalytic potential of the genotype. We will have now to discuss to what extent the above-mentioned concepts are equivalent, and to what extent they are not. In the next sections of this chapter we will try to determine the exact meaning of the term "genetic information" as implied by these concepts in order to eliminate some serious misunderstandings provoked

[126] See Piaget (1971/82). The terms "diachronic" and "synchronic" are particularly adapted to be used in the context of developmental events and functional events, respectively. But like the terms "homeorhesis," i.e./'stabilized flow" and "homeostatis," i.e., "stabilized state" (Waddington, 1968/12), they are not specific enough and may be used in reference to the non-epigenetic, non-functional and non-developmental events as well.



First position	Second position U	Second position C	Second position A	Second position G	Third position
U	phe	ser	tyr	cys	U or C
	leu	ser	f-s	try	A
	leu	ser	f-s	try	G
C	leu	pro	his	arg	U or C
	leu	pro	gln	arg	A or G
A	ileu	thr	asn	ser	U or C
	ileu	thr	lys	arg	A
	met	thr	lys	arg	G
G	val	ala	asp	gly	U or C
	val	ala	glu	gly	A or G

Ⓐ

Triplets	Two strands of the DNA code	Left chain a	b	c	d	e	f	Right chain g	h	i	j	k	l
	A:T	Thr	Pro	Arg	Cys	Ala	Pro	Trp	Gly	Ala	Thr	Arg	Gly
	C:G	Val	Cys	Val	Met	Cys	Val	His	Thr	His	Tyr	Thr	His
	C:G	non	Asn	Thr	Ser	Glu	Asn	Ile	Leu	non	Ser	Val	Leu
	G:C	Leu											
	T:A												
	G:C												
	T:A												
	A:T												
	A:T												
	C:G												
	T:A												
		downward reading			upward reading			downward reading			upward reading		

Ⓑ

Fig. 7.6 The "genetic code".
A - "Messenger RNA"(mRNA) codons for basic aminoacids. In mHNA molecules uracil(o) constitutes the complementaiy pyrlmidine base for adenine(A) instead of thymine which is characteristic component of the native DNA molecule. (After Bernal 1967, K.g. 16)
B - The intrinsic ambiguity of DHA molecule "encicode". The eleven nuoleotides long segment of the double helix may be decoded in twelve different ways. In vivo only one chain (strand) is selected for transcription,the starting point and the direction of the transcription being rigorously controlled.

by a non-consistent usage of the term "heterocatalysis," the term "potential" and the term "information."

Let us start our discussion on the nature of the "genetic code" with the following quotation which illustrates the present state of mind among biologists:

> "Those who object to the terminology of biochemical genetics as being anthropomorphic (Chargaff, 1963) and consider its use one indications of an epistemological twilight of science (Chargaff, 1970) might also take exception to the application .of the terminology of the secret writing of man to the biological processes of transformations and transmission of genetic specifications. However, the use of the terms "alphabet" and "words" in relating nucleic acids to protein synthesis (Gamow, 1954) propositions of various form 'codes' (Gamow, Rich and Yeas, 1956) and the use of the term 'code1 for an RNA template in protein synthesis (Crick and Watson, 1956) -- 'cipher' would have been the correct designation -- indicate that the early theorists of protein synthesis were aware of the compelling formal analogy between voluntary human and involuntary genetic cryptography. Conversely, the author of an elementary text on cryptology (Karai, 1967) has discussed the nucleic acid 'code of life1 in his treatment of the art of secret writing" (Hahn, 1973/8).

Hahn, in fact, explicitly states that his treatment of the subject should not be understood as made

> "for the purpose of injecting teleological or anthropomorphic speculations into molecular biology, but rather for the evident reason that the task of transforming and transmitting a linear set of symbols, comprising a meaningful text, is practically accomplished according to certain common logical principles..." *(ibid.)*[127]

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[127] In order to understand better the nature of the "genetic code," we will quote (after Hahn, 1973) the definitions of some terms used in the reference to this code:
Plaintext = The message which is put into secret form by transformation.
Code = Codes operate on plaintext groups of variable length: codegroups or codenumbers replace entire plaintext elements.
Cipher = Ciphers operate on plaintext units of regular length, in the simplest form on single letters of an alphabet. In the genetic "code" the basic unit of the plaintext is the single aminoacid.
Ciphertext = The final enciphered message transmitted.
Superencipherment = The result of an additional coding of a placode by a second transformation.
Encicode (from enciphered code) = The ciphertext resulting from a superen-cipherment.
Cleartext = The plaintext message transmitted without encipherment, i.e., in "clear" or plain language.

(contd.on page 176)

The DNA double helix molecule constitutes a pair of extremely long polynucleotides. From the purely chemical point of view, the molecule constitutes a "whole." From the cryptographic point of view, this molecule constitutes two completely different messages. Each one of the two polynucleotide chains might be translated into completely different sequences of aminoacids and each one of them might be read out in six different ways (see Fig. 7.6).

Let us now assume that the whole enzymatic machinery of an organism is composed of five thousand polypeptides, each one characterized by different sequences of aminoacids, different folding, and different length. If the giant DNA molecule is supposed to contain the whole "information" concerning the aminoacid sequences in each one of the different enzymatic proteins, and a single aminoacid is represented by three consecutive nucleotides (a triplet), the DNA molecule should be at least three times longer than the whole length of our five thousand polypeptides.

But what constitutes a "unit" message in the DNA "ciphertext"? Certainly neither a single nucleotide nor a single triplet. The unit cannot be conceived as something less than the code for a whole enzyme. If we will assume that the average enzymatic polypeptides are about 100 aminoacids long, the "ciphertext" unit must be composed of about 300 successive nucleotides. Because however seldom, if ever, a single polypeptide constitutes sufficient enzymatic machinery for a given synthetic pathway (see, for instance, the synthetic pathways represented in Fig. 7.5), the DNA "ciphertext" unit should be conceived as a long segment of molecule carrying the encoded information for several enzymes. The process of decoding must then consist in the simultaneous translation of the message for a group of enzymes.

(contd. from the page 175)

Encipherment = The procedures by which the plaintext is converted into the ciphertext.
Decipherment = The procedures by which the ciphertext is converted into the plaintext in routine instances in which the key is available.
Substitution Transformation = One of two general types of encipherment in which one set of symbols is substituted for another set of symbols, the sequence remaining the same.
Placode (from plain code) = The result of encoding the plaintext by only one transformation; also the intermediate result of the partial decipherment of a superenciphered code.
Superencipherment = The result of an additional encoding of a placode by a second transformation.
Encicode (from enciphered code) = The ciphertext resulting from a superencipherment.

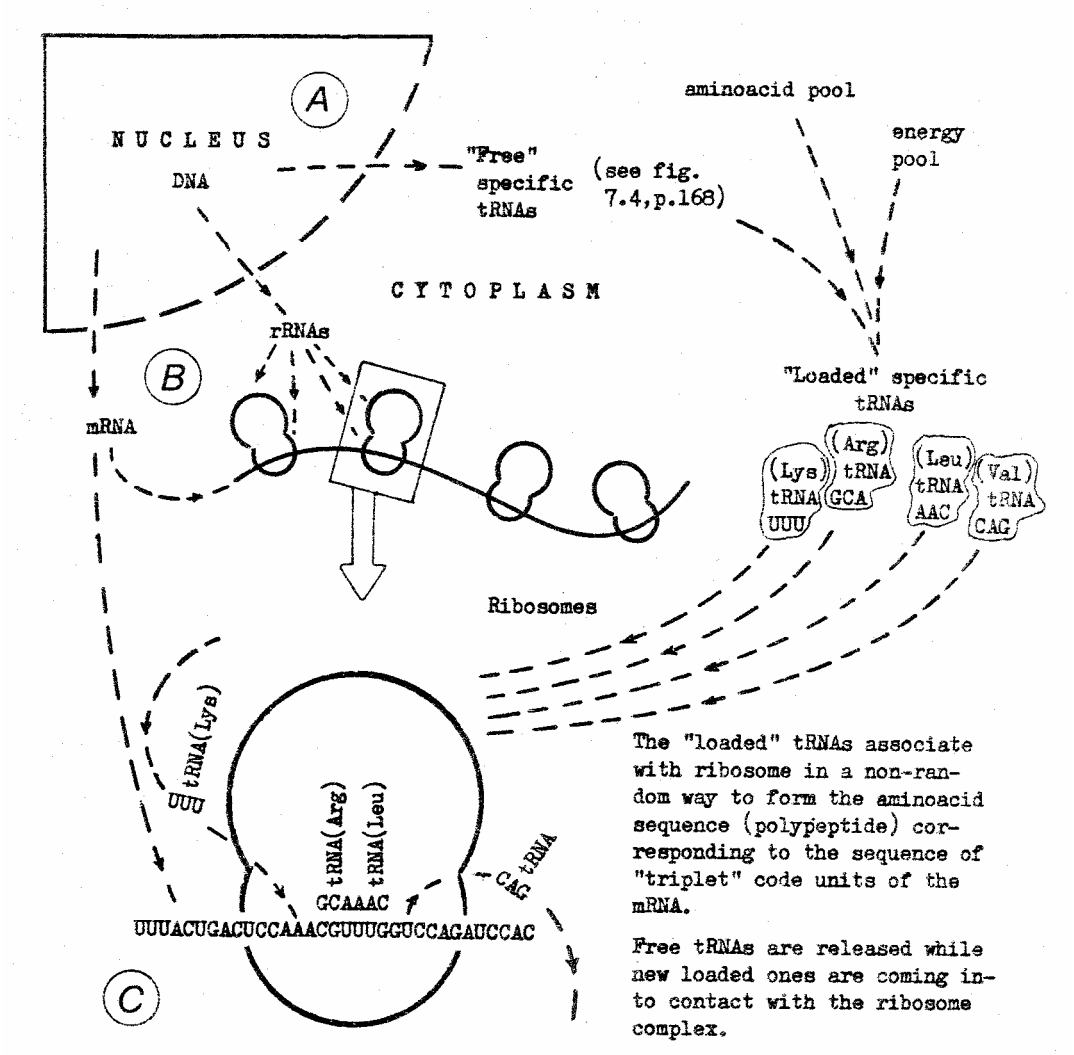

Fig. 7.7 Schematic representation of the current concepts of protein synthesis.
A - The molecules needed for the formation of the riboeome's translating and synthesizing machinery together with the molecular coded messages leave the nucleus where they were transcribed in a non-random way,
B - According to the message the translating machinery arranges the "loaded" tRNAs into the proper sequence.
C - The aminoacids are polymerized into a single polypeptide chain. (After Novikoff and Holtzmann 1970, fig. II-15)

After these preliminary explanations let us reflect upon the model of DNA code translation. This model incorporates the extremely heterogeneous evidence gained during the observation of in vivo production of viral molecules and upon rather indirect inferences from

other fields of biological and biochemical investigation. The details of this model may undergo some considerable modifications, but the general idea seems to be already definitely correct. How might the basic, elementary principles of cryptography be applied to the process of protein synthesis? We will reverse the order of discovery and before we discuss the details of the physico-chemical model of protein synthesis *in vivo* we will describe the application of the cryptographic terminology to the main stages of this process.

First of all, the synthesized protein molecules have to be considered as the "cleartext," for the proteins constitute the functional structures of the body. The DNA molecule residing in the nucleus of the cell has to be conceived as a sort of "ciphertext." It conveys a message, but the message is not functional in the form of the DNA molecules. The message hidden .in the DNA may become functional in the form of a protein molecule through the process of "decipherment." The process of "decipherment" consists in transforming the sequence of codegroups into the sequence of basic units of the plaintext. The basic unit of the protein plaintext is a single aminoacid. The single codegroup in the DNA consists of three successive nucleotides. In other words, the sequence of "triplets" along the DNA single chain corresponds to the sequence of single aminoacids in a protein molecule.

In the case of "genetic code," we have to do with superencipherment. That means that the DNA triplets are transformed first into the mRNA triplets, and these mRNA triplets are translated, according to the code, into the "plaintext" of a given protein aminoacid sequence. Now let us have a look at the actual process of protein formation.

7.8 The process of protein synthesis

The main stages of DNA partial transcription (into mRNA) and the consecutive translation of the transcribed segment are as follows:

(1) Selected segments of the DNA double helix uncoil

(2) Selected strand of the uncoiled segment becomes available to the pool of four ribonucleotides (A, U, C, G) which are arranged along it forming the complementary sequence

(3) The complementary sequence is polymerized by a specific enzyme, the energy of ATP molecules is functionally released during the formation of each dinucleotide.

(4) The newly-formed mRNA single strain is separated from its DNA template

(5) The mRNA strand migrates (or is transported) to ribosomes and is attached there in a non-random way (see fig. 7.7)

(6) The ribosomal machinery advances mRNA's codons (triplets) one by one exposing them to the anticodons of tRNAs (see fig. 7.7)

(7) Twenty different forms of tRNA carrying their specific aminoacids are attached one by one to the ribosome in the sequence determined by the sequence of mRNA codons (see fig. 7.7)

(8) Two neighboring tRNA molecules are functionally activated by the release of ATP energy "quantum" so that the polypeptide bond is created between the aminoacids they carry (see fig. 7.7)

(9) The unloaded tRNA floats away, the mRNA chain is advanced by one codon, and a new tRNA from the pool is attached to the ribosome in the liberated acceptor site (see fig. 7.7)

(10) The polypeptide, when finished, floats away ready to be inserted (according to its properties) into a proper place of cellular structure.

(See Mahler and Cordes, 1971/914ff.; Reithel, 1967/202ff.; Herskowitz, 1973, Yost 1972/526ff.; Noll, 1965/67-113; Whitehouse, 1971).

Practically all these stages are reproducible in a properly devised and controlled *in vitro* system. The term "control" means the non-random determination of the compounds present in the solution at the given moment of the chemical procedure, the proper sequence of changes in the concentration of the interacting chemical molecules, the proper sequence of changes in the concentration of specific ions, in the level of pH and temperature. Finally, all this non-random set of physical conditions gives the final result which may differ (and in practice does differ) considerably in the speed of the overall process and the purity of the yield from the results of the analogous process in the living cell. In the living cell, in fact, the speed of the protein synthesis, the practically absolute purity of the product, and the utmost economy in the utilization of energy sources strongly suggests that in the living cell the above process goes on on a non-random basis. In the case of the in vitro systems, because of the practical difficulties in controlling the movements, spatial orientation

and dynamics of single molecules, the process is only statistically effective. The essential principles of the process in both cases are, however, essentially the same. Our idea of the nature of the protein synthesizing system of the living cell is thus essentially correct. Every new piece of evidence carries us farther away from the random model. It is difficult to imagine that this trend might be reversed in the future.

In the past, the postulate of random mechanisms has been pushed towards lower levels of the observational scale, because of the growing awareness that the higher levels are observationally non-random both in their structure and their dynamics. Today, the process is reversed completely. On the molecular level, the idea of randomness has shrunk considerably. The aminoacid, sugar, lipid molecules, enzyme molecules, enzyme complexes represent, without any doubt, the highest possible level of order (repetitivity). This fact determines our ideas about the synthetic processes which produce them. The random models are now transferred to the "Middle Kingdom" of the so-called "self-aggregation" processes which we shall discuss in one of the subsequent sections.

7.9 The problem of integration during the protein synthesis

Before we start discussion of the origin of higher levels of cellular organization, let us reflect for a while upon some problems raised by the previously presented scheme of protein synthesis.

a) The problems involved in Phase (1):
The separation of complementary chains of the DNA double helix is not understandable in terms of intrinsic properties of the molecule itself (see section 7.3).

Unlike in the case of "self-replication," the separation of chains is supposed to be partial, i.e., the major part of the whole double helix is believed to remain "zipped." The selection of the proper segment of the molecule and the nature of the process which allows the partial longitudinal split cannot be explained or reduced to the intrinsic nature of the DNA molecule itself (see Fig. 7.1).

b) The problems involved in Phase (2):

The two chains of DNA are complementary but not identical. One of them might be compared to a "positive," another to a "negative," photographic picture. During the second phase .the proper chain has to be more available to the pool of free RNA nucleotides than the other ("negative") one. This availability cannot be reduced to the intrinsic properties of the DNA molecule itself.

Unlike the "self-replication," the "transcription" supposes the presence of free RNA nucleotides. The process of transcription, then, presupposes a non-random control of the environmental sphere (see Section 7.2), which cannot be dependent upon the intrinsic properties of DNA double helix, which in both cases is identical.

c) The problem involved in Phase (3):

The single RNA bases have to be polymerized together. This process presupposes a non-random activity of a special enzyme, or an enzymatic complex.

d) The problems involved in Phase (4):

Even supposing that the separation of the newly-formed mRNA molecule is spontaneous, its migration to the ribosomes where it will be "decoded" cannot be attributed either to the intrinsic properties of the DNA molecule or to intrinsic properties of the mRNA molecules.

e) The problems involved in Phases (5), (6), (7) and (8):

The process of the attachment of the mRNA molecule to the ribosome and the process of the attachment of the tRNAs to the successive triplets of mRNA is,possibly to a great extent, spontaneous. Still, the presence of the loaded tRNAs and the procession of mRNA triplets through the ribosome structure cannot be attributed to the intrinsic nature of the code, but it presupposes a functional release of energy. The origin of ribosomes constitutes a problem on its own.

f) The problems involved in Phase (9):

The "emptied" tRNAs have to be replenished. The replenishment of the "emptied" tRNAs cannot be explained without recourse to the non-random set of events, which are not reducible to the structure of the DNA molecule alone.

The nature of this process is unknown.[128] The process of the arrangement of newly-formed protein molecules will be discussed in the section on ''self-aggregation."

Additional remarks:

a) The division of the whole process described above into ten phases is completely arbitrary. As it would not be practically possible (taking into account

our present fragmentary knowledge of facts) to describe every event which takes place during the process of reading aloud a written text (the movements of the eyes, the biochemical processes in the eye retina, the whole pathway of sensory impulses within the brain, the way

[128] Taking into account the extremely high turnover rate of.cellular RNA molecules, the transcription of the DNA code for their de nova production has to be relatively fast. "Assuming that the numbers of genes per liver cell are 330 (rRNA=ribomal RNA), 1660 (5sRNA) and 13,000 (tRNA), the individual genes are transcribed twice a minute (rRNA), once a minute (tRNA) and once every 2.5 minutes (5sRNA). The magnitude of this transcription activity is even greater when one considers that the half-life of liver ribosomes is 5 days and tRNA 4-5 hours" (Thrasher, 1971/154).

in which the tongue, laryngeal and mouth muscles are activated...and so on) so it is impossible to produce an exhaustive redescription of all the biochemical processes which are indispensible for the proportionate, repetitive and functional production of protein molecules (even if a simplifying assumption that the functional enzymatic and structural complexes are made exclusively from the polypeptides were true, which it is not).

b) The scheme of the "ten phases" does not illustrate the complex transformations of free energy of the compounds involved in the process. It does not illustrate the indispensible regulation of the environmental parameters (the complex dynamics of pH level, of the complex dynamics of ion and buffer systems) , nor the complex dynamics of the metabolic pathways which provide the necessary "raw" material of smaller organic molecules, or degrade the already "used," "worn" ones.

c) The scheme does not show that the process of heterocatalytic activity (the production of polypeptides) involves not only the DNA molecule but also a great number of heterogeneous and intrinsically complex molecules which act in a concerted, non-random way.[129] DNA, no doubt about it, is a sort of code, but so is the RNA messenger molecule. The "translating" devices are no less complex and no less necessary than the DNA molecule. The matrix case with letters arranged
in it is not enough to explain how millions of copies of a journal appeared in
the hands of citizens. The idea of the genetic code only means that:

1) three successive nucleotide bases of DNA molecule happen to determine three successive nucleotide bases of mRNA;

2) three successive nucleotide bases of mRNA happen to determine which tRNA will be attached to it in the ribosome.

[129] "The DNA does not totally specify the epigenetic or any other biological process. There are initial conditions, unspecified by the DNA which operate as constraints also. The DNA is designed to operate in a particular cellular environment, on which it is dependent" (Goodwin, 1970/5).

But there is no physical law which would enable us to reduce the whole story to the sole existence of a DNA molecule, and its intrinsic physico-chemical properties. It is the biosynthetic system taken as a whole which provides the physically coherent and rational basis for the explanation as to how the functional proteins are appearing de novo in a repetitive way. In this sort of system there is no place for such questions as, for instance: "Which part of it is the *most* essential?"

It would be meaningless to maintain that the mainspring is more necessary for the movement of hands in a wristwatch than one of the wheels which transfer the energy of the mainspring to the balance wheel. We may rightly say that the energy of the mainspring is transmitted to the balance wheel and not vice versa. But we cannot say that the process of transmission is dependent more on the mainspring than on any other part of the watch machinery. In fact, whichever part of this machinery is missing or deformed, the whole process will come to a stop.[130]

In the case of the life cycle we have to do not with structures but with processes. Structures constitute an element, a necessary but not sufficient element of the processes. These processes as we have seen may be classified as functional processes, as developmental processes and non-developmental epigenetic processes leading to the appearance of the hereditary "individualizing" traits. As we have seen earlier, the genotype (or the genome) agency was postulated as a sort of transspatial and transtemporal constraint which explains the logically inevitable increase of complexity during the multiplication of bodily structures. Would it be right to recognize the above genotype's properties (implied by the Postulate of Heterogeneity) in the structure and the role played by DNA during the process of protein synthesis?

7.10 The DNA and the Postulate of Heterooatalysis

We should ask now whether the DNA molecule fulfills the criteria set

[130] A word of explanation is needed here. The DNA molecule does have some specific properties which make it exceedingly fit to play the role of an "information store." In this respect it is really marvelously "adapted" to the "needs" of the whole cellular system of processes. Weisskopf has speculated upon the particular properties of DNA and he has shown how clever was the Natural Selection, if one dare to say so, to select it for the role of a template (1969/38). However, even if we admit that the DNA molecule is a sort of marvelous structure, there are others too in the same cell. The whole is not less marvelous than one of its parts, to say the least.

by the Postulate of Heterocatalysis. How to answer this question? The Postulate was introduced under the impact of the direct evidence concerning the repetitive epigenetic phenomena of the life cycle. Which element of the protein synthesis is epigenetic?

The polypeptide chain is formed from the simple inorganic elements selectively absorbed from the organism's surroundings. These simple elements are linked together in complex units. An obvious increase of complexity takes place. A functional, concrete structure of polypeptide chain constitutes an incredibly small fraction of physically possible units which might have been produced from its constitutive parts. And so the criteria of an increase in complexity are fulfilled (see section 3.21). What is more, the production of functional polypeptides is repetitive in its final results. Because of it, the above epigenetic process cannot be attributed to random physical influences.

The production of the protein molecules does not start with the transcription or translation steps. It starts with the selective absorption of the originally random matter from the organism's surroundings. The composition of the proper polypeptide sequence is one of the advanced stages in the whole process. The whole process is most certainly non-random and functional. This presupposes the appropriate structures and the non-random control of the internal environment of the living cell. The origin of all these systems is obviously dependent upon the coexistence of many heterogeneous chemical compounds, organized in the non-random pattern.

The DNA molecule constitutes only a passive piece of the machinery. The genotype was supposed to provide a transspatial and transtemporal set of constraints which would explain the epigenetic process in a theoretically adequate way. The DNA molecule provides the set of constraints for the arrangement of free nucleo-tide bases, but the execution of this constraining role is determined by a complex non-random set of events which postulates (because of its repetitivity) a far more complex set of constraints.[131]

Of course, if the DNA molecule will be changed,the sequence of amino-acide within the polypeptides and consequently the properties of the protein molecules will necessarily change, too. This happens, for instance, when an alien DNA (or mRNA) is injected into a cell by a viral complex particle. But

the substitution of the original DNA by the viral DNA might be compared to the substitution of a printing-plate cylinder in an offset printing machine. The printing-plate cylinder alone is completely incapable of producing a single copy of print. The integrated action of the whole printing machine is needed here. Similarly, the production of viral structures which follows

[131] "Molecular biology speaks of a program inscribed in the nuclei of the egg-cells from the start of the ontogenesis [life cycle]. However what is involved is more than just a program and a code, there is still the transcription, decoding, and translation of messages transmitted from the nucleus to the cytoplasm to be considered" (Wolff, 1970).

the injection of the viral DNA molecule into a cell cannot be attributed to this DNA molecule alone, but it presupposes a non-random, although patholologically deviate operation of the protein-producing machinery of the cell.

7.11 The DNA and the Postulate of Stability

The phenotypic structures undergo a constant and non-random motion. Upon the molecular level this motion is manifested in the form of the metabolic turnover phenomena. Upon the organellar level constant developmental and functional transformations take place. All these different forms of motion and their repetitivity create a question-raising evidence and postulate a stable agency controlling all these motions and independent from these motions at the same time.

The genotypic agency, as we have seen (see section 6.7) is expected to constitute an intrinsically stable entity, immune from the environmental influences . In which sense does the DNA molecule fulfill this criterion set by the Postulate of Stability of the Genome?

The above question may be further divided into two parts. First, we may ask to what extent the DNA molecule retains its integrity during the whole life cycle. Secondly, we may ask to what extent the DNA molecule remains stable in its dynamic properties. The entitative instability and impermanence would of course affect the dynamic stability but not necessarily *vice versa.*

The entitative permanence of the DNA molecule is often expressed in terms of genetic Central Dogma on the one hand, and in terms of irreversibility of mutations on the other. The Central Dogma's essential feature "is the oneway flow of information, a flow which is never reversed" (Stent, 1970).

$$\text{DNA} \rightarrow \text{RNA} \rightarrow \text{protein}$$

The Central Dogma is not a physico-chemical notion. In fact, there is no physical law which might exclude the possibility of reversal of the translational processes. The Central Dogma was postulated in order to stress the stability of native DNA and its role as the ultimate controller

of the life phenomena.[132] The biological domain which was most affected by the interpretational consequences of the Central Dogma was immunology. Some relatively simple organisms were shown to be able to produce an incredible number of specific antibodies against an incredible number of antigens (see Haurowitz, 1969/63; Kolata, 1974). Antigens, because of the purely speculative validity of the Central Dogma, were held to be incapable of "informing" the DNA molecules, and thus incapable of determining the specific sequence and configuration of antibody polypeptides. So, a sort of genetic paleontological "memory" had to be postulated, and the specificity of the antibodies were explained by a sort of evolutionary "reminiscence." It was postulated that an organism had met the concrete antigen in its past history, and it "remembered" its configuration in the form of a specific DNA segment which is reactivated during the immunological reaction (see also Richards et al., 1975/135).

The recent discovery of the enzyme known as reverse transcriptase has undermined the validity of the Central Dogma. The situation at the moment is rather complicated. Some authors, as for instance Hahn, consider the already known mechanisms engaged in the one-way translation (from DNA to protein) as completely unfit to operate in the opposite direction.

> "One would need to postulate an entirely different and separate biochemical machinery for 'reverse translation,' an unlikely prospect …"
> "...It appears, therefore, that the key statement of Crick's (1958) Central Dogma which holds that 'once information has passed into protein it cannot get out again' will remain valid and can now be reiterated on safer grounds 15 years later since the mechanistic details of the translation machinery have become better understood" (1973/9-10).

Herskowitz, on the other hand, states that the enzyme capable of the reverse transcription has been discovered in non-pathological mammalian cells (1973/63). This fact might suggest that the reverse flow of "information" does take place *in vivo.* However, the tests of the enzyme (reverse transcriptase) activity are not decisive because the assay of the enzyme is effected upon the synthetic systems in vitro (see Nature, June 9, 1971).

The irreversibility of random mutations constitutes an equally unclear

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[132] Black discussing the Central Dogma writes:' "A dogma may be defined as an "arrogant declaration of opinion,' and ignoring any apparent arrogance in these assumptions made by the molecular biologists, it is clear that their own use of this term is simply an admission that they are faced with the old scientific dilemma of 'proving a netative': the eternal problem of proving that what has never been observed, could never be, or could never have been observed" (1972/ 117).

domain of various and contradictory opinions. Since the discovery of the special cellular mechanisms capable of repairing some forms of DNA injury (see Whitehouse, 1969/323ff.; Hanawalt, 1972; Woodcock and Grigg, 1972; Herskowitz, 1973/128ff.), the previously observed cases of the reverse mutation received a new empirical support. The existence of the DNA-repairing enzymatic system may be interpreted as an argument for the essential dependence of protein-producing system from some higher and more complex (than DNA alone) mechanisms of the cell. It weakens the thesis about the intrinsic stability of the DNA molecule and its role as the ultimate safeguard of repetitivity of life cycles. The functionality of the DNA-repairing structures puts forward the problem of their epigenetic origin, and multiplication, which brings us back to our original question of the transspatial and transtemporal integrating constraints.

The dynamic stability of DNA constitutes an even more complex problem. First of all, both the translation and replication, as we have seen, necessarily postulate that the DNA is undergoing some rather dramatic transformations. None of these transformations is determined by the intrinsic properties of the DNA molecule. The stability of the dynamic pattern of these transformations cannot be then explained in terms of the DNA molecule properties. If the Postulate of Stability has any sense at all, it cannot be based solely upon the role played by the DNA molecule in the life processes. Some other heterogeneous structures are involved here too. Their epigenetic origin is beyond any doubt. So here again we are hitting the "stone wall" of epi-genesis and its mysterious repetitivity. Everything we know about the DNA and its role in the life processes seems to constitute a new "question-raising" evidence, and none of the three main genotype's postulates find their adequate fulfillment in the properties of this compound.

In the final part of our essay we will discuss some theories concerning the intrinsic organization of epigenetic phenomena of the life cycle. There are three such theories. One is the theory of Jacob and Monod, and it is expected to explain how different segments of the DNA program are available for transcription in a non-random temporal sequence. The second theory tries to give the answer to the question how do the protein molecules join together into functional structures. That is the theory of random self-aggregation. Finally, there is a theory which tries to explain how the supramolecular complexes come together and form the spatially integrated micro- and macroscopic functional structures of the living body. That is the theory of "fields and gradients."

From the philosophical point of view, the evaluation of these theories should consist in determining whether they are or are not circular. They should not be accepted as "question-solving" concepts unless they do not rely upon the non-random, epigenetic, developmental phenomena. If they do, we are still closed within the "question-raising" conceptual framework. It is doubtful whether a final demonstration of the validity or invalidity of these theories might be carried out at this stage of our knowledge. In the last chapter we are only going to stress some crucial elements of the whole problem, without however being able to provide the decisive judgment about the "question-solving" value of these theories.

CHAPTER EIGHT

PHENOTYPE-GENOTYPE (GENOME) DICHOTOMY:

FUNDAMENTAL RELATIONSHIP OF LIFE PROCESSES

OR FRAME OF MIND?

8.1 The phenotype-genotype dichotomy and the reductionist (monist) doctrine

Having in mind the already known details of the polypeptide synthesizing machinery, we may realize that the DNA molecule does not fulfill the criteria set for the postulatory genome's agency (see chapter six). First of all, the DNA molecule does not copy itself so it fails to fulfill the Postulate of Autocatalysis. Secondly, the DNA cannot be considered as an active element in the process of polypeptide construction, although it "guides," in the passive sense of the word, some steps in this process. So it fails to fulfill the role of an active integrating constraint during the "life cycle." Finally, the DNA molecule is not stable at least in the sense that during the "life cycle" it undergoes structural modifications irreducible to the intrinsic physico-chemical properties of the molecule itself.[133]

In 1967 Bernal wrote:

> "In the present state of our ignorance we may regard the gene either as a tiny organism which can divide in the environment provided by the rest of the cell; or as a bit of machinery which the 'living' cell copies at each division" (1967/245).[134]

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[133] "Les problèmes soulevés par la DNA restent nombreux et difficiles. Chargaff (1968) en a très bien résumé l'essentiel:

1° Quelle est la structure du DNA lorsqu'il il fonctionne, intact, dans la cellule?
2° Q'est-ce qu'une "molecule" de DNA?
3° Quelle est la structure d'une nucléoproteine?
4° Quelles sont les forces qui maintiennent la structure native du DNA?
5° Comment une protéine reconnaît-elle la sequence d'une acide nucleique ou un nucléotide?
6° Des chromosome differents d'un même noyau cellulaire contiennent-ils le même DNA?
7° Quelle est la séquence des nucléotides dans le DNA?

A une ou deux exceptions près, ce sont déja les questions que se posait Miescher, en 1869, a Tübingen, chez Hoppe-Seyler, lorsqu'il découvrit la 'nucléine'!" (Louisot, 1972/87).

[134] The theory which identified the genome with the DNA molecule has led to terminological ambiguity. The term genotype (genome)' may denote today (a) an arbitrarily selected hereditary trait existing within the broader context of an individual "life cycle"; (b) an abstract, statistical average quantitative value of the genome in the sense (a) registered within a population; (c) a postulatory entity which fulfills at least three main Postulates of the Genome, i.e., the Postulate of Autoreplication, the Postulate of Heterocatalysis and the Postulate of Stability; (d) the main bulk of the cell's DNA as distinguished from smaller DNA molecules detected in some cellular organelle such as mitochondria, chloroplasts and so on (see Campbell, 1969).

The "environment provided by the rest of the cell" refers, of course, to a non-random idea of complex physico-chemical conditions constituting the essence of the "question-raising" element of the genetic theory. The circular nature of the above illustrated explanatory idea seems evident.

Earlier, in 1961, Commoner had written:

> "...the unique capability of living organisms for self-duplication and inheritance arises from complex multi-molecular interactions among at least several classes of cellular components. Neither DNA nor any other cellular component is a 'self-duplicating molecule' or the 'master chemical of the cell'...There is no evidence from recent investigations of the biochemical aspects of genetics which requires abandonment of the conclusion, long established by biological data, that the least complex agent capable of self-duplication is the intact living cell" (see also Markert, 1963, and Bonner, 1971/xv).

Commoner distinguishes three possible forms of the explanation of the "life cycle" phenomena. The first, which he considers as "untenable," would be a sort of "mystic non-material 'vital force' which supposedly animates the otherwise dead substance of the cell" (1964/365). The second answer might take the form of a "special cellular component which possesses the fundamental attribute of self-duplication and which is therefore a 'living molecule' and the basic source of the life-properties of the cell." Finally, the third answer would amount to the recognition that:

> "The unique properties of life are inherently connected with the very considerable complexity of living substance and arise from interactions among its separable constituents which are not exhibited unless these components occur together in the complex whole" *(ibid).*

If it were correct to claim that the "whole cell," or rather the "whole life cycle," constitutes the proper explanation of hereditary phenomena, the distinction between the phenotype and genotype would become a sort of solely methodological, speculative tool. In fact, the phenotype would play the role of the genotype.

At first sight this sort of explanatory structure evokes in the mind the logically erroneous *idem per idem form* of explanation. However, the contemporary speculative effort made to fulfill the reductionist program and to save the monist axiom (see section 6.11) is based upon such a complex empirical and

speculative pattern that the theory which virtually eliminates the real distinction between the phenotype and the genotype should be taken seriously into consideration.

The main theory of this kind is the model of "Teleonomic Mechanisms in Cellular Metabolism, Growth, and Differentiation" commonly referred to as the Monod and Jacob model of gene regulation. For the sake of terminological simplicity, we will refer to this model as TTM (Theory of Teleonomic Mechanisms).

This theory is closely related to the complementary theory of self-aggregation of macromolecular structures. We will refer to this second theory as TSA (Theory of Self-Aggregation).

In the first part of this chapter we will analyze the essential conceptual and empirical elements of both theories. In the second part we will try to draw some conclusions concerning the explanatory value of both theories.

8.2 Theory of Teleonomic Mechanisms (TTM)

The theory (see Monod & Jacob, 1961/397ff.) is an application of control theory and the feedback concept to the processes of protein production *in vivo.*[135]
The theory tries to provide the answer for the non-random sequence of synthetic steps observed during the single life cycle of single-celled organisms. The living organism functions in a non-random way. This, as we have seen (section 5.8), necessarily postulates a trans-temporarily and trans-spatially integrated set of synthetic steps during which the inorganic material "sucked" from the surroundings is changed into functional structues of the living body. The TTM does not explain the trans-spatial integration of the functional bodily structures. This integration is supposedly explained by the theory of self-aggregation (TSA) which we are going to discuss in one of the following sections. The TTM tries to provide an answer to the question: What determines the strict, repetitive sequence of synthetic steps leading to the appearance of the elements constituting these functional structures? In other words, TTM is supposed to provide the explanation of the "epigenetic integration." What are the essential elements and premises of the theory?

The production of a structural element Alpha, which constitutes a part

[135] The non-random production of proteins in vitro may be exemplified by the Merrifield method (1968). It is an extremely complex procedure. The non-random attachment of a single aminoacid to the polypeptide chain requires about 100 different operations.

of the functional structure F_{AB}, requires a number of synthetic steps, during which "precursors" of Alpha are gradually formed (see, for instance, Fig. 3.7).

Each synthetic step requires the activity of a specific enzyme. Consequently, the specific enzymes have to operate in a proper sequential (temporal) order. According to TIM, the trans-temporal integration of the enzyme's activity may be reduced to the right temporal order in which the enzymes are produced. As the specific polypeptide molecules constitute the indispensable component of enzyme molecules and the structural characteristics of polypeptides are supposed to be encoded in a segment of the DNA molecule, TTM assumes that the whole problem of the epigenetic integration can be explained by temporarily ordered molecular signals which switch on (induce) or switch off (repress) the right segments of the DNA double helix.

The problem of regulation of temporal pattern in which the different enzymes start working may then be interpreted in terms of the temporal pattern in which different segments of DNA molecule (supposedly containing the information for the specific sequence of enzyme polypeptides) are selected[136] for transcription.

Now we may ask how the signals are temporally ordered and how they induce or repress the right segments of the DNA molecule. According to the theory, the signals are identical with some "precursors" produced by the enzymes. These products are assumed to diffuse from the point where they were synthesized[137] so that they eventually collide with the proper "recognition site"

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[136] "The term "selection" is closely related to the notion of epigenesis. It refers to a dynamic process which is repetitive. The "selection" presupposes that out of more than one possibility, one only is repetitively observed to come into effect. The notion of the number of possibilities available, together with the notion of the repetitive appearance of the same dynamic pattern leads to the question about the nature of "constraints" obviously limiting the originally non-univocally determined situation. The notion of "selection" does not presuppose a "non-deterministic" system of entities, but it does presuppose the really random original conditions. It means that the term "selection" (as well as the term "epigenesis") may be correctly used whenever a dynamic event was occurring repetitively, but the starting conditions of this event were different in each case.

[137] The process of diffusion conceived in terms of "random walk" operating on the basis of intrinsic termal jumps of individual molecules necessarily implies that the signals are numerous, that they move out from the spatial compartment in which they were produced and that the proportion of "wrong" ineffective collisions with different structures of the cell exceeds by several orders of magnitude the number of the effective collisions. In this way, the "precursor," which plays the role of the signal, will not be further "developed" (because it has wandered away from the synthesizing machinery), or the synthesizing machinery and the precursor meet by chance. The possibilities of this meeting are determined by the concentration of the enzymatic synthesizing complexes, by the concentration of the precursor-signals, by the dimensions of the spatial compartment in which the process of diffusion takes place, tu mention only the most important parameters.

somewhere within the complex system of the double helix DNA molecule. The term "recognition" means that the stereochemical properties of the signal determine the unique "fit" with the proper recognition site. In this way, any danger of inducing or repressing a wrong site is physically excluded. Once the "recognition" has taken place, the dependent segment of DNA is activated, its transcription and translation starts, and a new set of polypep-tides is produced. This new set of polypeptides forms (spontaneously, according to TSA) the next segment of the synthetic pathway, so that the "precursor" which has triggered the whole reaction may be further processed and the epigenetic process goes on through a number of consecutive steps coming closer to the level of the functional structure. A new form of "precursor" is formed. This new "precursor" switches off the previously activated segment of DNA and switches on the new segment of the "genetic code." The enzymes produced during the preceding stage are decomposed, while the new set of polypeptides is formed.

The TTM necessarily postulates a specific organization of the DNA molecule. In 1960 Jacob, Perrin, Sanchez and Monod introduced the notion of the "operon" which is crucial for the proper understanding of the above regulatory mechanisms.

The "operon" is believed to constitute a rather long segment of the DNA molecule in which the following parts may be recognized:

(1) a segment in which several "cistrons" are encoded. A single "cistron" (up to ca. 2000 nucleotide pairs long) codes for a single popypeptide. The “operon's” segment embraces the number of "cistrons" corresponding to the number of different specific enzymes engaged in a single biosynthetic pathway. Some enzymes are composed of several non-identical polypeptides, so that the number of "cistrons" in an operon may exceed the number of enzymes encoded in it.

(2) a segment in which the "operator" gene is located. The "cistrons" can not be transcribed unless the "operator" is in the active state.

(3) a segment in which the "regulatory gene" is located. The regulatory gene is supposed to produce a specific substance which if joined by an "inducer" or a "represser" molecule is capable respectively of "opening" or "closing" the operator gene, and in this way it can start or suppress the transcription of the given set of "cistrons."

As in the case of the genetic code, similarly in the case of the "operon" concept, we are not interested here how it happened that a given "represser" or given "inducer" structure "fits" to the structure of an "operator" gene. In Monod and Jacob's opinion *"any* physiologically useful regulatory connection...might become established by adequate selective construction of the interacting sites..." (1961/391) and the term "selection" refers here to the random influences implied by the concept of Natural Selection. As we have already stated in the first chapter of our essay, we do not enter into the discussion of evolutionary "possibilities" or "impossibilities" if there are any.

(4) a segment called "promoter" which separates the "operator" gene from the dependent "cistrons" and constitutes a sort of punctuation mark from which the transcription (from DNA to RNA) starts.

We cannot discuss the details of the whole model. It would take up too much space. But the general idea is this. The Monod and Jacob theory is devised to explain the epigenetic phenomena of the life cycle. The DNA molecule is transmitted from the parental organism. In the first stage, a number of its "operons" is guiding the production of some polypeptides. These polypeptides come together (see TSA), forming an enzymatic complex capable of carrying on several synthetic stages during which precursors of "medium range" organic "precusor" molecules are fabricated. When the concentration of a given "precursor" reaches a certain limit, the concentration gradient and the particular structural properties of the end-product switch off the previously activated operon (or set of operons) and at the same time another operon (or set of operons) is switched on. The "precursors" have to reach a proper "recognition" site somewhere along the giant DNA molecule, but this is supposed to happen by simple diffusion of free molecules without recourse to any guiding or transporting agency. In this way different segments of the DNA molecule become available for transcription into mRNA, and this happens in a non-random way, for the preceding step determines in a univocal manner the next one.[138]

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[138] 0ne thing seems to be rather obvious. The postulatory mechanism of "adaptation" through Natural Selection, which constitutes the basis for the interpretation of the results obtained by population geneticists should be carefully revised and accordingly adjusted (see Reznikoff, 1972/133). The mutational random influences upon an operon are expected to be disastrous in a high majority of cases.

> "If the order of aminoacids is disturbed by mutations, the lack of fit among the produced structures is inevitable, the developmental character of a concrete morphogenetic pathway can be almost completely destroyed (see Stebbins, 1972/85).

The Monod and Jacob model does not explain the spatial arrangement of the produced protein molecules. But, it is supposed to explain the temporal order of their production. Is this model satisfactory? At present our knowledge about the details of biochemical events is still very fragmentary. However, the elements included in the idea of the operon are not sufficient to provide the adequate physicochemical explanation of the process. First of all, the functional release of energy is necessary for successful transcription and translation. This, of course, postulates an adequate control of the energy-releasing system. The hypothesis of the simple osmotic phenomena which transport the inducing or repressing agents to their corresponding "recognition" sites is to be evaluated in reference to the empirical data concerning the speed of the observed events and the concentration and heterogeneity of different chemical compounds coexistent in the cell in every moment of its existence. Independently of the actual observational evidence, one may ask whether the random movements (of the Brownian movement type) might be considered as satisfactory explanation. We should remember that a bacterial cell is capable of replicating all its extremely complex machinery together with its DNA molecule in less than half an hour.[139]

8.2 Theory of Self-Aggregation (TSA)

In the preceding section we were discussing the mechanisms postulated to explain the non-random appearance of different forms of polypeptides during the "life cycle" of a cell. But the process of formation of separate polypeptide molecules does not answer the question as to how they are functionally integrated in space. There is a theory, based upon considerable empirical evidence, which says that once the proper set of protein enzyme molecules is produced they arrange themselves in a sort of "production line," because their structure allows a unique fit of the interlocking parts (see Berill, 1971/21ff.; Yost, 1972/854ff., and Pollard, 1973/369ff.) In other

[139] At 37° the complete sequential replication of *E. coli* DNA takes approximately 40 minutes -- the cell may double every 20 minutes (see Donachie et al, 1973/10).

words, the produced proteins will move at random until they join together as jigsaw puzzle pieces (see Weissmann, 1970/156) because only one integrated spatial pattern is supposed to be thermodynamically possible in the given environment, or rather thermodynamically stable. And this one happens to be functionally correct (see also Anfinsen, 1973). All the other spatial patterns are supposed to be unstable, so that the given, concrete set of enzyme molecules will remain separated until they will finally lock together in a functionally perfect complex. Once this functional spatial pattern is achieved, the sequence of the reactions catalyzed by this complex will be predetermined by the spatial organization of its parts.

Now, the mechanisms postulated by Monod and Jacob are supposed to regulate the temporal pattern of the different polypeptides' production, and the self-aggregation phenomena are supposed to lead to the temporal regulation of the sequence of biosynthetic steps within a given biosynthetic pathway. The unique "fit" of the enzymes within a given complex is determined by the unique sequence of aminoacids which in turn is determined by the sequence of triplets along the proper segment of the DNA molecule. In this way, the self-aggregation is assumed to be reducible to the pattern of DNA molecule triplets.

Putting everything together, we can realize that TIM and ISA are intrinsically linked together and that they in fact constitute a complementary set of theories.

TIM explains the formation of enzymatic, functional complexes which produce the "medium range" organic molecules necessary for the production of higher macromolecular structures.

Both theories form then a sort of complementary conceptual framework which according to Monod explains adequately the main problems raised by the non-random phenomena of the "life cycle."

> "Qu'on analyse les fonctions catalytiques ou régulatrices ou épigénétiques des protéines, on est conduit àa reconnaître qu'elles reposent toutes et evant tout sur les propriétés associatives stéréospécifiques de ces molecules ... C'est donc, comme on le voit, la somme, ou plutôt la coopération d'un tres grand nombre d'interactions ... intramoléculaires, qui stabilisent la structure fonctionelle ...
>
> .,.Le mécanisme de formation de ces structures est au-jourd'hui assez bien compris dans son principe. On sait en effet:
>
> 1. que le déterminisme génetique des structures de protéines spécifie exclusivement la séquence des radicaux amino acides correspondant à une protéine donnée;

> 2. que le fibre polypeptidique ainsi synthétisée se replie spontanément et de façon autonome pour aboutir à la conformation pseudo-globulaire, fonctionelle" (Monod, 1970/106ff.).

Yates et al. seem to interpret correctly Monod's ideas when they write:

> "Monod...claims that the molecular theory of the genetic code does today constitute a general theory of living systems" (1973/111)

The "genetic code" means the DNA molecule. Its structure determines the sequence of aminoacids in the polypeptides, and this in turn determines the functional properties of the polypeptides. These functional properties enable the polypeptide molecule to carry on the synthesis of organic molecules and to aggregate into more complex structures of the living cell.

At the end of section 8.2 we have already mentioned some rather weak points of TTM which might eventually become strengthened or, on the contrary, even more undermined by the forthcoming evidence. Now let us try to evaluate both TTM and TSA in a more systematic manner.

Our criticism will be concentrated around the two basic questions:

> (1) Are the "Teleonomic Mechanisms" adequate to provide an ultimate explanation of the non-random "life cycle" phenomena?
>
> (2) Is the random self-aggregation theory compatible with the observed dynamics of cellular and supracellular development and function?

A theory or a model may be considered as incorrect because it does not give the proper answer for a given detail, although it is right as far as basic principles are concerned, or, on the contrary, it might provide the right answer for a given detail, but remain unsatisfactory upon the level of the overall pattern of phenomena. In the concrete case of genotype-phenotype relationships, the TTM and TSA might be approximately correct, which would mean that they need only a further development, but they give an essentially sound explanation of the dynamics of the life cycle. But it might be that the theories may provide a satisfactory answer for some phenomena of the life cycle, without, however, reducing the main "question-raising" element of the phenotype's dynamics, or even forcing us to postulate such mechanisms which amplify this "question-raising" rather than diminish it.

How will we carry out our critical evaluation of the two above-mentioned theories? First we will make a sort of review of critical comments expressed among biologists on the subject. These critical comments may be summarized under a few main headings.

a] Firstly, some facts postulated by the TTM do not find experimental confirmation.

This sort of failure is relatively insignificant in itself. If it were the only weak point, the theory as such might survive, although some minor modifications might be needed.

b] Secondly, the TTM seems to be inadequate to explain the epigenetic phenomena upon the level of multicellular life cycles.

If this sort of criticism is valid, the TTM may remain as adequate for the unicellular life cycles. In this sense, the DNA might be rightly conceived as the genotype of the phenotypes whose "life cycle" remains always upon the level of the single cell structure.

c] Thirdly, the TTM seems to be inadequate to explain the epigenetic phenomena even upon the level of a single cell life cycle.

If this criticism is valid, the DNA and the mechnisms postulated by TTM may remain as an element of question-raising evidence of the life cycle without, however, providing us with a hint where to look for the true source of trans-spatial and trans-temporal integrating constraints.

We will now discuss briefly the examples of the above three forms of criticism directed against the TTM.

8.4 Contemporary criticism of the Monod and Jacob model of gene regulation

Independently of the problem of intrinsic coherence and plausibility of TTM, the empirical confirmation of the assumption that the mechanisms postulated by Monod and Jacob actually regulate the non-random sequence of "cell cycle" structural transformations is still lacking. The notion of repressers and activators as postulated by the Jacob and Monod model still suffers the inadequate biochemical confirmation. In other words, the postulated specific substances responsible for repression and/or activation are difficult to trace. Noll writing about failures to isolate as recognizable molecular entities the repressors and activators postulated by Monod and Jacob states:

> "Heretical minds began to question whether these failures might not be attributable to the possibility that these factors do not exist in the form originally contemplated rather than to experimental difficulties" (1965/107; Weissmann, 1970/155).

Donachie and collaborators openly state:

> "There is at present...no information about the spatial or temporal control of the enzymes directly concerned with the major events of .the cell cycle"

(1973/27; see also Paul et al, 1970/237-8).[140]

Another group of critics points out that because the Monod and Jacob model of gene regulation was originally designed to explain phenomena of the bacterial "life cycle," some authors protest against the application of the phenomena observed at the higher levels of life. The extrapolation from fragmentary and uncertain (see above a]) evidence concerning bacterial organisms to the level of multicellular organism is in the opinion of many authors completely unwarranted. The criticism dates from the early sixties. Holtzer denounced rather strongly the

> "article of faith...summarized in the axiom that anything found to be true for *E. coli* must also be true of elephants (Monod and Jacob, 1961)" (1963/127).[141]

Schjeide and De Vellis wrote:

> "Some investigators are of the opinion that there is insufficient evidence for the existence of the repressors of the genome in higher organisms and that it is foolhardy to make extrapolations from *Escherichia coli* to human beings" (1970/12; see also Paul et al, 1970/241; Brachet, 1971/263; Weissmann, 1970/155; Bonner 1973/ 3; Littlefield, 1970/447).

Finally, the structural elements constituting parts of the Monod and Jacob model are considered by some authors as intrinsically deprived of the potential attributed to them by TTM. This form of criticism concentrates predominantly upon the intrinsic inadequacy of the DNA macromolecule system. Several authors stress the need for supramolecular regulatory mechanisms explaining the non-random activation of different portions of the DNA molecule's program (see Nanney, 1968; Subirana, 1970/248; Nozeran, 1971/2; Schjeide and De Vellis, 1970/13; Markert and Ursprung, 1971/92, 119).

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[140] "Control theory fails in two respects: First it does not respect the test of matching which says in effect …: an ant cannot control the behavior of a horse unless you make very particular arrangements for him to do so...Second, control theory cannot assure the biologist that the way an 'ideal' controller might work is in fact the way a biological controller does work" (Yates et al, 1972/116).

[141] Holtzer makes allusion here to the following text: "If the codes in *Serratia* and *Escherichia* and perhaps a few other bacterial genera turn out to be the same, the microbial-chemical-geneticists will be satisfied that it is indeed universal, by virtue of the well-known axiom that anything found to be true of *E. coli* must also be true of Elephants" (Monod and Jacob, 1961/393). *Serratia* together with *E. coli* belongs to Eubacteriales. The above remark of Monod and Jacob, if judged from the context in which it was pronounced must be interpreted in the sense of a deliberate exaggeration testifying to the awareness that the extrapolation is illegitimate, although it may serve as a postulate to be verified. Commoner, on the other hand, rightly criticized the overstatements of such popularizers of biological progress as I. Asimov, for instance (1961).

Lederberg writes:

> 'The point of faith is: make polypeptide sequences at the right time and in the right amounts, and the organization will take care of itself. It is not far from suggesting that a cell will crystalize itself out of the soup when the right components are present" (1966/x).[142]

Yates et al state:

> "Monod's thesis for evolutionary development assumes the invariant reproduction of DNA. However, this invariance involves arrangements of components including repair enzymes and polymerases. Beyond the invariance of DNA lies another system with invariances" (1972/112) .[143]

Herskowitz discusses the up-to-date empirical evidence concerning the "life cycle" control under the following headings/statements:

> "Gene replication is regulated at the cellular level in procaryotes." "Gene replication is also regulated at the cellular level in eucaryotes." "Nuclear genome number is regulated at the tissue and organ levels." "Gene destruction is normally programmed." "Disproportionate nuclear gene replication occurs and is presumable regulated genetically" (1973/391ff.).

All the above statements refer to the DNA molecule, and/or to the chromosome structure. We have to stress this point because it is clearly far from being certain whether the Genome's Agency may and should be identified with the DNA or chromosomes.

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[142] "The propositions [which] represent the view with which modern biology approaches the problems of the living cell...may be summarized crudely by saying: Given the genes, you have the enzymes; given the enzymes you have everything else..." (Rainer, 1968/34). Ramachandran points out how many physico-chemical parameters decide about the conformation of the polypeptide chain. Primary structure [the sequence of aminoacids] is only one of them. Even single aminoacids within the polypeptide may accept different stereo-isometric forms (1969/79ff.; see also Anfinsen, 1973). In this sense the configuration of aminoacids within a polypeptide chain is not fully determined by the sequence of triplets of the DNA "genetic code."

[143] "Many other biologists have recently expressed misgivings about the adequacy of the DNA code to deal satisfactorily with all the phenomena of development, and more particularly, with stages beyond the translation into protein structure; that all else follows automatically is a gratuitous assumption that leaves some of the most difficult problems of development untouched" (Foulds, 1969/310),

"It has sometimes been assumed that certain enzymes appearing during development of differentiation are the initiators of a particular differentiation. It is like putting the cart before the horse" (Schjeide and De Vellis, 1970/30).

We might ask whether the concept of the "precursors" appearing during the process of gradual differentiation of the cell and "controlling" the further differentiation does not deserve the same kind of criticism.

> "Among organisms having DNA as genetic material, some can regulate their chromosome morphology, all seem able to modify the chemical composition of their DNA. through en-zymatically directed, unique modifications of the bases. Organisms having DNA genetic material also use various means to regulate the synthesis of DNA" (Herskowitz, 1973/398).

Finally, the same author states that

> "the crossing-over and synapsis are under genetic control ... [and] that the genotype controls or regulates the oc-. currence of point mutations" (ibid. 405) ."[144]

All the above-quoted statements mean that the DNA and its adjacent structures (histones, nucleoproteins) are repetitively modified, changed by a proportionately complex system of agents. It is difficult to say which elements of the cell do not participate in this system of gene control.[145] But one can hardly doubt that a significant part of phenotypic structures temporarily appearing during the "cell's life cycle" is participating in this regulatory mechanism. Consequently, the concept of the genome's agency in the sense determined by the Postulates of the Genome becomes closer to the rede-scription of the totality of structures recognizable during the whole "life cycle."

At the same time, it becomes more and more obvious that the Postulate

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[144] The terms "control" and "regulation" are used in contemporary molecular biology with two different meanings: (1) to "control" or to "regulate" may mean that a specific functional (in the sense described by Riggs, 1967) regulatory mechanism exists which preserves the homeostasis of a given system; (2) these terms may simply refer to the fact that an entity present in an *in vivo* or *in vitro* system (a molecule, a set of molecules) in a given state influences in the physico-chemical sense a functional or developmental mechanism. In this latter sense the "controlling" or "regulating" factor does not constitute a necessarily part of the functional system, but simply affects its dynamics. A change in the environmental temperature may thus affect the speed of an enzymatic reaction and so "control" it. An inorganic randomly organized substance in the environment of a cell may affect its intrinsic dynamisms, and if the behaviour of the cell is non-random, the inorganic substance is sometimes referred to as a "controlling" or a "regulating" factor.

The above ambiguous terminology may create some serious misunderstandings as to the role played by different substances during the "life cycle" phenomena and as to the value of some physico-chemical relationships invoked to explain the phenomena of life.

[145] "As an embryo develops, the information in the genome of the fertilized ovum is progressively and systematically unlocked and relocked as the daughter cells of each division progressively move into slightly different environment which they themselves are helping to create" (Willmer, 1970/573).

"...it must be appreciated that the cell is an integrated, multiphase, multicomponent system in which the various components are geared to each other. Hence it is likely that any dramatic alteration in any one factor, such as a great change in cyclic AMP activity, can occur only in conjunction with changes in other cellular systems" (Chayen and Bitensky, 1973/663).

of Stability loses its empirical background.[146] We will return to this particular point later. At the moment let us turn our attention to the critical discussion of random motion phenomena upon which both TIM and ISA are founded.

8.5 Random thermal molecular dynamics and its explanatory value in genetic theory

Both TIM and TSA clearly admit that the trans-temporal and the trans-spatial integrative ordering processes do take place during the cell's "life cycle." This process, of course, has to be explained by an appropriate dynamism of real entities. Both theories assume that the living cell at any, arbitrarily selected stage of the "life cycle" is entitatively constituted by a set of molecules (inorganic molecules, "medium size" organic molecules, macromolecules and macromolecular complexes). In other words, neither of these theories considers the cell as a complex but as a single chemical compound. The dynamic processes which are manifested by the intrinsically heterogeneous but repetitive sequence of transformations which form the units of "life cycles" is explained in terms of the preexisting structures of the earlier stages and the random thermal dynamics of the molecules within the cell. The signalling molecules, for instance, are not transported or guided to reach their "targets." The idea of the directed transport or guidance would not only make the postulatory mechanism too complex, it would also raise new questions of the origin of the transporting (or guiding) mechanisms, and it would even make redundant the requirement of the specific stereochemi-cal "fit" between the signal and the recognition site. So the thermal, "random walk"

[146] The only molecular component of the cell which was expected to fulfill the Postulate of Stability was found to undergo some significant changes during the life cycle (see Adrian, 1971; Herskowitz, 1973/217). "...Viola-Magni (1966) found as much as 32% of the DNA of the nuclei of the adrenal medulla was lost from the nuclei but was re-formed when the stress [cold stress] was removed (also see Pelc and Viola-Magni, 1969). The whole subject of metabolic DNA and of changes in the amount of DNA per nucleus induced by cellular activity in response to hormones, has been much studied by the Belgian group under Fautrez and Roels in Ghent. According to this group, the DNA content of a nucleus is not strictly constant; rather it is an equilibrium value around which significant variations occur (Roels, 1966)" (Chayen and Bitensky, 1973/63).

of the free molecules in the fluid medium is believed to constitute the main dynamic element of the process. But here precisely seems to be the weak point of both theories. TTM does not provide us with any hint as to how after the collision between the specific signal and the proper recognition site the rest of the processes necessary for the production of polypeptides takes place. All the process of activation of the given operon, its transcription, its translation remains as mysterious as before.

The specific signals are assumed to be identical with the "precursors" of the functional structures. Their diffusion "in search" of the "recognition site" makes them wander away from the site of their origin, and so being dispersed more or less randomly all over the cell space they are not readily available for further transformation into the functional structures. The signalling based upon the random diffusion seems extremely uneconomical and it necessarily postulates that the majority of the signalling molecules is randomly distributed in relation to their own synthesizing machinery.[147]

The TTM does not explain what sort of dynamism drives and integrates functional events necessary for the transcription and the translation of a given set of cistrons into polypeptide molecules.[148]

Virtually the same problems may be raised in reference to the Theory of Self-Aggregation. As the separate randomly distributed polypeptides

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[147] Schjeide and De Vellis, for instance, turn our attention to the fact that

> "the explanations based upon the control theory conceptual framework imply an astonishingly large variety of signals...in different systems and in different phases of development. It is possible that the factors regulating cell differentiation are so many, diverse and subtle that a useful degree of comprehension of their natures may never be forthcoming..." (1970/13).

From our scheme of the minimal set of events implied in the developmental process (see Fig. 5.7), one may easily calculate that if specific molecular signals were really responsible for the trans-spatial and trans-temporal regulation of the development, they will constitute at least 501 of the different heterogeneous molecular forms distinguishable during the "life cycle."

[148] Waddington makes an important distinction between the concept of induction and the concept of the transmission of an organization (1966/106). This distinction is close enough to our distinction between the "triggering" activity and the "developmental event." As Bunge rightly points out: "seulement des changements peuvent avoir une efficacité causal" (1971/129). The "activity" of an "inducer," a "represser" or a "trigger" is not necessarily a *causal* activity. The transformations of the "life cycle" have to be explained by truly causal mechanisms.

do not constitute physically adequate synthesizing machinery, they have to be integrated in more complex structures together with heterogeneous non-protein co-enzyme groups. This integration may of course occur by random collisions. But the random collisions necessarily yield many other nonfunctional structures, complexes. It is rather doubtful that in vivo processes are compatible with the presence of the number of non-functional structures which would necessarily originate if the process of aggregation was operating upon the basis of random collisions. Further observational data will solve this question sooner or later.[149]

Finally, the random, thermal collisions do not seem to provide sufficient energy to produce the chemical- links necessarily implied during the synthetic processes of the "life cycle." In the in vitro experiments, the energy-rich compounds such as ATP are used as the energy source, but the experimental reports clearly show that these energy-rich compounds are supplied in amounts many times greater than physically necessary.

The TTM is intrinsically related to the theory of self-aggregation. The polypeptide chain alone .does not make sufficient machinery for the non-random production of "precursors" and the final functional structures. The theory of self-aggregation invokes essentially the same dynamic elements to answer how the formation of functional structures is effected. It relies upon the thermal collisions of polypeptide molecules. The real value of this theory will depend on the outcome of the experiments which will answer to what extent it is true that:

> (1) the "random walk" of the polypeptides and other organic molecules *in vivo* might really lead to the origin of structures stable enough to operate as a "production line" for the synthesis (or breakdown) of other organic molecules.

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[149] The Jacob and Monod model may finally be confirmed by the empirical evidence. But we may ask ourselves, whether the model is not based upon a *"petitio -principii"* fallacy. In a way the complex pattern of postulated inducers and/or repressors evokes essentially the same problem as that stated forty years ago:

> "When we discover ... the existence of an intraprotoplasmic enzyme or other substance on which life depends, we are at the same time forced by the question how this particular substance is present at the right time and place, and reacts to the right amount to fulfill its normal functions. It is always, therefore, to the conception of life as a whole that we are driven forwards" (Hal-dane, 1931/79).

(2) the "random walk" yields the structures which are sufficiently ordered to explain the observational precision of the *in vivo* synthetic processes.[150]

(3) the "random walk" dynamics operates within the time range which is comparable to that of the *in vivo* processes.

At the moment it is difficult to give the definitive answer for the above set of questions. [151] However, the widespread utilization of "high energy" compounds during the metabolic processes of the cell makes the "random walk" model rather unlikely. The problem is extremely complicated because it cannot be excluded that the diffusion processes, the, "random walk" phenomena, are to a certain extent exploited during the processes of in vivo. To decide whether they are really sufficient or to the contrary that they are not sufficient may be really difficult, simply because of the technical difficulties involved in the reconstruction of the actual mechanism.[152]

8.6 Recent vitalist-ie trends in theoretical biology

If our critical remarks concerning the explanatory validity of TIM and TSA are justified, what sort of more general conclusions might be drawn from the present up-to-date knowledge and understanding of the "life cycle" phenomena? In sections 5.8 and 5.11, we have presented the apparently necessary notion of trans-temporal and trans-spatial constraints ultimately responsible for the repetitive sequence of the transformations observed during the continuous process of generation of living beings. The main question

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[150] Sleigh (1973/537) recalls experiments carried out by Wolpert and collaborators (1964) on isolated fractions of *A. proteus*. The cytoplasmic extracts separated from nuclei, food vacuoles, and most of the surface membranes did not show any traceable activity. If, however, the ATP was added, the movements, streaming and similar phenomena were observed. How to interpret such results? To what extent are they analogous to Galvani's and Volta's experiments on the influence of the electric current on vivisected muscles and nerves of the frog?

[151] Although it is already proven that essentially random collisions may lead to the reconstitution of rather complex structures, such as, for instance, the structure of some virus molecules, it is also true that in vivo the process which leads to the arrangement of "mature" virus particles is not random or spontaneous, except in a few stages (see Berill, 1971/32-33).

[152] The speed of the overall process is such that a theory of random collisions, especially if we take into account the extreme heterogeneity and variety of elements tightly packed within the miniature cell space, looks, at least superficially, unconvincing. However, such theoretical calculations as for instance Pollard's (1973/366ff.) suggest the "random walk" model should be carefully evaluated.

seems to be this. Is this concept of constraints entitatively integrated or, to the contrary, might it be divided among different physical elements identifiable or with the separate coexistent complex structures constituting a given stage of the essentially trans-temporal "life cycle" pattern, or even with some parts of such stages?

Beckner states the above question in the following manner:

> "What distinguishes living from non-living things? The first — answer is: 'A complex pattern of organization in which each element of the pattern is itself a non-living entity.' In this view, a living organism, and each of its living parts, is exhaustively composed of inanimate parts: and these parts have no relations except those that are also exhibited in inanimate systems.
>
> "[The second answer:] 'The presence in living systems-of emergent properties, contingent upon the organisation of inanimate parts but not reducible to them'...[this answer] 'holds that the parts have relations in the living system that are never exhibited in an inanimate system.
>
> "The third and least fashionable answer is: The presence in the living system of a substantial entity that imparts to system powers possessed by no inanimate body..." (1967/253ff).

Later on, Beckner summarizes Driesch's concept of

> "an autonomous, mindlike, nonspatial entity that exercises control over the course of organic processes; it is not actuality or activity in Aristotle's sense."
>
> "Driesch admits that the laws of physics and chemistry apply to organic changes ... Although each event [observed within the 'life cycle'] is physico-chemical, it is subject only to *post hoc* explanation in physicochemical terms. 'The entelechy influences the course of [biological processes] "suspending" and "relaxing" the rather vast range of possibilities inherent in the physical entities constituting a given structural form of the body ... the entelechy [postulated by Driesch] operates in the region of possibilities left open by the operation of [physical laws]" *(ibid.)*
>
> "Most of scientific criticism of vitalism points out that vitalism provides nothing more than pseudoexplanation" (Beckner, ibid.; see also Simon, 1973/4).

However, we must admit that vitalism does not seem to be properly refuted so far. Vitalist opinions are recently represented by Elsasser and Polanyi. Monod provides us with the short and admirably clear resumé of Elsasser's opinion.

> Sans doute les propriétés étranges, invariance et téléonomie ne violent-elles pas la physique, mais elles ne sont pas entièrement explicables à l'aide des forces physiques et interactions chimiques révélées par 1'etude des systèmes non vivants.
>
> II est donc indispensable d'admettre que des principes, qui viendraient *s'ajouter* à ceux de la physique, opèrent dans la matière vivante mais non dans les systèmes non vivants ou, par conséquent, ces principes électivement vitaux ne pouvaient pas être découverts. Ce sont ces principes (ou lois biotoniques, pour employer la terminologie d'Elsässer) qu'il s'agit d'élucider" (1970/41).

The essential elements of vitalist opinion one may recognize in the writings of another physicist, Michael Polanyi (see 1968/1308ff).

Ruse discussing *practical* impossibilities of "ever providing a complete physico-chemical analysis of the organic world (at least in the foreseeable future)," adds:

> "The question arises of whether such a complete physico-chemical analysis is ever possible even from a *theoretical* viewpoint. [Ruse admits that although] few biologists can be found to give any support to vitalism, ... the reason for this is not so much that a belief in such forces is contradictory, but rather that their existence or non-existence seems totally irrelevant to the biological endeavour. The forces are undetectable, they are not subject to experimental control, and everything they were invoked to explain seems entirely explicable in some other way - a way not involving a commitment to the forces" (1973/209).

If Ruse is right in claiming that really "everything they were invoked to explain seems entirely explicable in some other way (presumably purely physico-chemical way) the idea of the genotype's agency conceived as essentially different from the physico-chemical manifestations observed within the "life cycle" is completely redundant. But Ruse's second argument which consists of the claim that the "forces" are "undetectable" and that "they are not subject to experimental control" does not sound convincing. Is the gravitational field directly detectable? In which sense might we claim that we are able to control the gravitational field? The manifestations of the gravitational field are obviously dependent upon many conditions which are experimentally controllable. In a similar' way some biological phenomena are controllable within certain limits. The introduction of the idea of the "gravitational field" has not stopped physical endeavour and was not irrelevant to the progress of physical sciences.

The consequences of introducing into the biological explanation of an idea essentially, entitatively and operatively' irreducible to the entities and operations immanent to inanimate matter would provoke incalculable modifications in our views on the natural world. The prospects for such a revolution are at present rather faint. But the decisive proof of reductionism is still lacking.

We may hope that sooner or later such a proof (or disproof) will be finally produced. In the final sections of our essay we want to present some possible directions of the further speculative research in this field. First we will try to restate in a more abstract way the fundamental "question-raising" features of the life cycle. This more abstract presentation prepares some background for the future, more precise and more conclusive insight into the nature of relationships between the phenotype's and the genotype's realities.

Further on, we will trace some descriptive and explanatory concepts developed in reference to the multicellular forms of life such as the concept of the morphogenetic field. These concepts illustrate some speculative trends which may in future become more precisely formulated and exploited.

8. 7 The "factorial" and "'holistic" form of reductionism

The facts and the concepts concerning the phenomena of the "life cycle", even in its simplest form of a "cell cycle", are desperately complex. We must ask ourselves once again whether the monistic metaphysical belief is strengthened by the discoveries of modern molecular biology, or if on the contrary some form or other of dualistic concept of life achieve more and more persuasive arguments in its favour. By dualism we simply mean a concept of life which is entitatively irreducible to the chemical structure and dynamics, however complex it may be. If the trans-temporal and trans-spatial constraints which constitute the "Smallest Sufficient Condition" of developmental events we have recognized within the phenotype's "life cycle" (section 5.11) could be completely described in terms of entities composed of atoms of inorganic matter, the monistic beliefs would have been considered as definitely proven. But this proof is still lacking. In order to see better the crucial element of the monistic-dualistic controversy, we may attempt to represent this controversy in a more abstract form so.that the essential points of the question will become more obvious.

The monistic doctrine insists upon the axiom which says that the causal explanation of the "life cycle phenomena" is *adequately* reducible to the properties of entitative elements composed from the atoms of inorganic matter (see section 6.11). The monistic explanation of the life cycle phenomena may be stated in two different forms. One form tends to identify a "factor" which makes part of the

greater coexistent structure recognizable during any arbitrarily selected stage of the "life cycle." We may call it "factorial" monistic explanation of life. It attributes some special, extraordinary properties to a physical element of the whole living entity.

The second form of monism which we might call the "holistic" explanation of life phenomena attributes the special self-replicative properties to the whole set of the structural elements coexistent within any arbitrarily selected stage of the "life cycle."[153]

The "factorial" form of monism necessarily leads to the distinction between the Postulate of Autocatalysis and the Postulate of Heterocat-alysis, for the "factor" has to copy itself, on the one hand, and to produce the whole structure of the living entity on the other.

The "holistic" form of monistic explanation virtually reduces the Postulate of Heterocatalysis to the Postulate of Autocatalysis. The whole set of entities engaged in the "life cycle" phenomena produces from the random matter and energy of its surroundings a new, numerically different but structurally and dynamically identical "life cycle."

We will try now to apply the previously defined concepts of the "life cycle," "epigenesis," "function," and "development" to the analysis of the explanatory value of both the above-sketched monistic explanations of life phenomena. This analysis does not pretend to resolve the problem of the validity of these monistic forms of interpretation of life. But we believe that it might help in preparing a conceptual background for a more precise and more accurate evaluation of these problems.

8.8 Abstract recapitulation of the "life cycle" causal problem

Because of the complexity of the empirical evidence and the consequent complexity of concepts involved in our speculations, two main dangers of such an analysis should be mentioned at the very beginning of our discussion.

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[153] Kornacker writes:

> "The problem of constructing a physical definition of life is particularly difficult, because any living organism can be represented as an aggregate of non-living atoms" (1972/1-2).

This statement is not correct. Any living organisms can be represented as a finite sequence of transitions from one structural stage into another, different one. Living organisms in their descriptive aspect might be defined as systems producing their own replicas from random inorganic matter. Life, then, is essentially the process of formation of self-replicating replicas. No single static structure, however complex, should be considered as a living body.

The first danger consists in the possibility that the concepts will not be precise enough, and the conclusions drawn would simply not hold.

The second danger arises when we attempt to make the concepts more clear and univocal which may lead fbut not necessarily have to) to such a simplification of the abstract notions that they will be deprived of any correspondence to the actual essential phenomena of life. In this second case, whatever might be the result of our discussion, the conclusions will not be applicable to our original problem.

In the case of such a simple "life cycle" as a procaryote life cycle, the basic unit of the evidence consists of the fact that a single bacterium produces it own, exact copy. To realize the nature of the causal question provoked by this fact, we have to admit that this process of self-copying is observed repetitively in the surroundings which are not repetitive.

At the time t we can observe the cell C in the surroundings E . At the time t we can see the two cells OC in their respective surroundings E -R-,, E -R,. The two cells are absolutely identical down to their molecular structure and dynamism. Their respective surroundings are not, however, identical. In spite of this at the time t~ we will observe four identical cells C+C+C+C, each one of them immersed in more or less different surroundings. The differences between the surroundings of each cell are commonly referred to as the "randomness" of E. The identity of cells is commonly referred to as "order" of living structures.

t_0	t_n	t_{2n}
(C)E_0	(C)E_0-R_1	(C)E_0-R_3
		(C)E_0-R_4
	(C)E_0-R_2	(C)E_0-R_5
		(C)E_0-R_6

During this transition, a new copy of the cell is produced. This copy is functional, i.e., capable of self-copying. This of course implies that the new set of functional structures was built from the environmental inorganic matter with the aid of the environmental energy. Both the matter and energy of the concrete surroundings are different in each case, and because of this we are faced with the production of order from disorder.

From our earlier analyses (sections 4.11 and 5.7) we know that the production of functional structures postulates necessarily the gradual, step by step, integrated construction of functionally impotent "precursors." So the transition from (C) to 2(C) necessarily involves a definite number of synthetic steps which may be calculated for a most successful "minimal" case but which is irreducible to a single step transformation (if the laws of chemistry are expected to be obeyed) .

At the same time we must remember that the functional events necessarily postulate heterogeneity of structures, and the observed re-petivity of functional events during the "life cycle" necessarily postulates coexistence of separate functional and non-functional structures.

Putting everything together, we have to admit that every structural non- random stage of "life cycle" is composed of many coexistent different entities, and the relationship of functionality can never hold between all of them. In other words, the analysis of the repetitivity of the functional event, together with the analysis of the developmental event, necessarily postulates coexistence within the sphere of the living body of non-randomly arranged and non-randomly behaving molecules which, however, do not take part in the functional events.

We may see now that what we call the "unit" of life does not consist of a particular static structure but of a series of transformations, intrinsically irreducible to a single transformation. This fact may be represented as follows:

t_0	t_{n-2}	t_{n-w}	t_{n-b}	t_n
O R	O R = order	O R = random	O R	O R
$(C)E_{0_1}$	$[C+(C-z)]E_0-R_z$	$[C+(C-w)]E_0-R_w$	$[C+(C-b)]E_0-R_b$	$2(C)E_0-R_a$
$(C)E_{0_2}$	$[C+(C-z)]E_0-R_{z_1}$	$[C+(C-w)]E_0-R_{w1}$	$[C+(C-b)]E_0-R_{b1}$	$2(C)E_0-R_{a1}$
$(C)E_{0_3}$	$[C+(C-z)]E_0-R_{z_2}$	$[C+(C-w)]E_0-R_{w2}$	$[C+(C-b)]E_0-R_{b_2}$	$2(C)E_0-R_{a_2}$

As we have seen, the element of order and the element of randomness are inevitably present upon any arbitrarily selected stage of the self-copying process. The pattern of transformation is, however, ordered as a whole. This means that the sequence of transformations is identical in spite of the fact that every single step of this transformation goes on within the random (non- repetitive) surroundings.

Let us consider now two neighbouring "quantic" structural stages of our abstract "life cycle."

$$[C+(C-x)]E_Q\text{-}Rx \quad \text{is transformed into} \quad [C+(C-x)+Rw]Eo\text{-}Rx\text{-}Rw$$

What happens between t_x and t_{x+1} ? An amount of randomly "organized" matter and energy, denoted on our scheme by R_W, enters the sphere of the living body which in the previous stage had the structural non-random form of [O(C-x)]. R_W is to be considered as random, because practically it is never the same in the case of many cells passing the same stage of "life cycle." So in different "life cycles" a concrete R_W is originally intrinsically determined (according to the physico-chemical laws) to a different spatio-temporal configuration. In spite of this, R_W becomes part of the identically organized spatio-temporal configuration, because the numerically different "life cycles" are structurally and dynamically identical. The "factorial" monistic theory would say here that R_W entered the sphere of the influence of the "factor," which constitutes a sufficient constraint to change the original intrinsic (random) determination of R_W into a new (ordered) determination of part of the living body.

The "holistic" theory would say that R_W has entered the sphere of the influence of the whole ordered structure of the previous stage of the "life cycle." This structure constituted the sufficient constraint which changed the original and random determination of R_W incorporating it into the ordered structure of the body.

According to the "factorial" explanation, a "factor" ranains stable throughout the "life cycle" but acts differently during every single stage of this "life cycle."

According to the "holistic" interpretation ordering operation of the living organism at every single stage is explained by the different structural and dynamic state of the previous stage.[154]

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154 "The simple view of the bacterial cell as a membrane enclosing a number of independently operating biochemical systems, each specified by the genome, has...been replaced by a more complex picture in which the organization and localization of certain complex enzyme systems within the cell envelope is of key importance in the regulation and integration of the major events in the cell cycle...at least some,of these components may prove not to be determined by the genome but rather by the pre-existing arrangement of the same components in parent cells" (Donachie et al, 1973/39).

We can see here how the idea of the genotype (genome) conceived originally as a central integrating agency is gradually dissolved and attributed to different subsystems of the whole organism.

Summing up, the process of self-copying necessarily postulates the incorporation of randomly organized matter and energy from outside and a gradual construction of functional structures. The process necessarily postulates repetitivity of functional events which are irreducible to the thermodynamic random collisions. It necessarily postulates that a considerable number of stages within one cycle of self-copying is fulfilled. It necessarily postulates the considerable molecular heterogeneity at every single stage. Finally, it necessarily postulates that a 'considerable part of the non-random structure at any arbitrarily selected stage of the "life cycle" is not functional but constitutes passive "precursors" gradually reaching the level of functional structures.

Are all these seemingly necessary postulates conciliable with the monistic restrictive axiom which does not allow us to postulate an integrating, ordering, intrinsically stable but operatively heterogeneous (in space and in time) agency not composed of inorganic atoms?

The "factorial" concept of monistic explanation which recently was proposed in the form of the theory of the "genetic code" does not seem to be acceptable, coherent and corresponding to the empirical data. But is the "holistic" explanation more successful and is it reconciliable with the empirical data?

If the correct answer is affirmative, the reconstruction of a living cell would consist of the formation of any arbitrarily selected structure constituting transient form of the whole set of transformations which we call the "life cycle." The problem is whether this concept of causal explanation of the "life cycle's" repetitivity is intrinsically coherent if the physico-chemical regularities were to be applied to the above abstract scheme of events. At the moment we are unable to provide the verdict.[155] What

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[155] "It is generally assumed that a living being is characterized by basic stability properties - regulative, homeostatic abilities -- which allow him to survive perturbations of the ambient medium ... I do not think that the known laws of physics and chemistry will suffice to give us the corresponding abstract knowledge of living beings for the following reasons:

(1) You cannot rely on the basic classical laws of statistical mechanics and theremodynamics, because these laws apply either to open homogeneous systems (statistical mechanics) or closed nonhomogeneous systems (thermodynamics), while living beings are open and nonhomogeneous systems.

(2) If you do not use basic laws, then you are obliged to use only physico-chemical laws involving local molecular effects; that is, in fact, what biochemists do now, with their use of individual models for enzymatic actions. The problem is to integrate all of these individual actions into a basic conceptual framework applicable to the dimensions of the molecule, the cell, the metazoa. We have to use a theory which describes individual molecular interaction and the basic effects of statistical thermodynamics in the same way. This is the aim of the theory of morphogenesis (in a rather generalized-sense) I plan to describe briefly. We know that in. a watch, the key works are the pendulum and the escapement; but do we know what are the key organs in a living being? At the cellular level the genetic material appears to be a likely candidate and its molecular structure is now well known. But do we know the corresponding abstract dynamic structure?" (Thorn, 1968/165).

we wanted to do was to create a reasonably clear concept of the problem involved in the above postulatory explanation.

It is needless to add that the concept of the genome would in this case be identifiable with any arbitrarily selected molecular structure which temporarily appears as the transient but coexistent set of chemical elements we call living body. The genome would be as changeable as the phenotype, and in fact, there would be no reason for introducing the distinction between the hereditary material and the phenotype. The notion of the "hereditary material" would denote only this part of the phenotype which at a particular stage of history was believed to incarnate the controlling agency of life phenomena, but which, upon a closer analysis, was re-dimensioned conceptually to the role of a dependent, fragmentary mechanism constituting a part of the self-replicating whole.

Is this view correct?
Is it really intrinsically coherent?

Before Carnot analyzed the cycle of events in an "ideal" engine, the theoretical or even practical efforts to construct the *"perpetuum mobile"* were legitimate. In the analogous sense it is legitimate today to believe that the already known or postulated physico-chemical mechanisms and phenomena do provide a scientifically acceptable conceptual framework which explains the repetitivity and integration of the life cycle without recourse to a dualistic idea of a mysterious entitatively (not only operatively) trans-spatial and trans-temporal, integrating, indivisible and unchangeable agency. But would it not be premature to claim that this monistic explanation of life phenomena will remain valid in the future?

Perhaps the necessary premises for the ultimate decision are already available.

In Carnot's time the awareness of the physical phenomena was certainly more fragmentary than it is today. Still, it was possible to reach a final conclusion which will remain valid independently of any newly-gained physico-chemical evidence. One might say that the level of our biochemical knowledge makes the situation ripe for a similar step in biology. But most certainly this step was not yet made. Just what sort of conceptual framework, what sort of speculative process will help us to evaluate the available evidence and to get the -decisive conclusion, it is hard to foretell.[156]

At the beginning of our essay (section 1.2), we decided to limit ourselves to the problems raised by the phenomena observed upon the unicellular level of life. (Of course, during our discussions, we have used, in order better to illustrate some basic biological concepts, the evidence concerning multicellular "life cycles"). The nature of the phenotype-genotype dichotomy and the nature of the adequate constrains explaining the repetiti-vity of the extremely heterogeneous pattern of the life cycle still remains, as we have seen, unsolved. Neither the Monod and Jacob model of gene regulation, nor the theory of self-aggregation fulfill the basic postulates provoked by the "question-raising" element of the unicellular "life cycle." At the level of multicellular "life cycles," the theoretical crisis is even more evident. Here some new concepts were developed in order to facilitate both the description and the explanation of the "life cycle" pattern. In the next chapter we will discuss some details of these concepts. This may help us to realize better the full depth of the darkness which still hides the correct and adequate explanation of the basic properties of living beings.

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[156] It seems that an analogous example may be provided by the history of the research oriented towards the establishing of definitive proof of the consistency of formal systems. Despite Hilbert's, Ackermann's, von Neumann's and Herbrand's efforts to secure a consistency proof of arithmetic, Gödel has demonstrated that the consistency of a formal system adequate for the number theory cannot be proved within the system (see Ladrière, 1957; Nagel and Newman, 1958; van Heijenhoort, 1967).

CHAPTER NINE

ON SOME ABSTRACT CONCEPTS OF INTEGRATION CONCERNING THE SUPRA-CELLULAR LEVEL OF "LIFE CYCLE" PHENOMENA

9.1 On the idea of the "morphogenetic field"

The case of a unicellular "life cycle" raises the question of an appropriate integrative causal explanation. The dynamic order of functional and developmental events postulates, as we have seen, a rather complex idea of constrains which does not seem to be adequately reducible to the conceptual framework of the Theory of Teleonomic Mechanisms and the Theory of Self-Aggregation.

At the level of multicellular "life cycles" the problem of integration of functional structures and developmental processes is even more complex and the current explanatory postulates are even more vague and inadequate.[157]
The central abstract concept in this domain is the idea of a "morphogenetic field" introduced by Gurwitsch (1922), Weiss (1923) and Rudy (1931).[158] The notion of the "morphogenetic field" deserves a separate epis-temological and methodological study. Here we will limit ourselves to the discussion of some essential elements of the concept. This analysis may help us to understand a general line of reasoning and the prevalent epis-temological tendencies characteristic of the actual state of biological speculative thought.
"Such processes [in - PL] which complex systems of order develop

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[157] The embryological development of an animal from a single cell into a multicellular organism remains as one of the least-understood areas in biology. All of the billions of cells of the adult organism presumably contain the same genetic information, and yet each cell type selectively expresses different, and relatively small, parts of its genetic potential" (Davidson, 1973/295. See also section 6.12).

Littlefield criticizes "a widespread and entrenched assumption that the 'problem' of differentiation is 'solved," and that embryogenesis is an understandable although elaborate program of sequential genetic activations, only the details of which remain to be put in order" (1970/439).

[158] See Weiss (1961/71) and Polanyi (1968/130ff.). Nicolet comments on the idea of "morphogenetic field" in the following way: "...At present, the results of experimental embryology are generally interpreted in the framework of the gradient field theory since it is so far the only developmental theory founded on some biochemical evidence...and we are unable to explain how such quantitative differences may lead to qualitative changes" (1970/260).

out of rudiments which have a much less complex and less obviously orderly arrangement" (Waddington, 1966/106) are the sort of direct observational evidence which call for an explanation.[159] In 1933 Waddington created a special term, namely "individuation," in order to distinguish these processes from the processes of "induction" in the sense of "evocation," i.e., simple triggering of a physical phenomenon or a series of physical phenomena.

> "I took the word individuation from psychology, where it is used to refer to the way in which what are originally a series of separate muscular contractions and movements of bones become gradually molded into a coordinated and skilfully performed single action. This seems to me to have considerable formal similarities to processes by which a number of separate discrete masses of tissue, such as lumps of bone, muscle, nerve, etc., become molded into a normally organized functioning limb or other anatomical structure" (ibid./106-107).

The processes of "individuation" (in Waddington's terminology) were commonly referred to as "field phenomena". It is clear that the termr "field phenomena" should be distinguished from the idea of those dynamic phenomena which are not producing an orderly integrated pattern.[160] The "field" itself is a sort of an "agency" (or "agencies") which provides causal explanation for the repetitive appearance of "integration" or "individualization" phenomena. Just as some of the physical phenomena are referred to as "gravitational," others as "electromagnetic" and it is a common belief among physicists that "behind" them a special kind of "field" exists, which "acts" in a sense more stable and unchangeable than the separate, concrete phenomena. This concept of a "field" in a way reduces the enormous variety of the phenomenal events to a relatively *simple* idea. But at the same time, the "gravitational field" and/or "electromagnetic field" are not "figmentum mentis," are not a sort of Platonic idea, but they share the same "status of reality" as the separate,

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159 "...One of the most dramatic manifestations of the 'field' principle in the 'self-organization' of organism...concerns the ability of a scrambled suspension of single cells from a fairly advanced embryonic stage to reconstitute themselves without specific .'inductive'guidance from the environment, into amazingly complete and harmoniously organized organs; e.g., liver, kidney, feathers, of the typical morphology and functional activity..." (Weiss, 1961/71).

160 "In some contexts the field is thought of as actually affecting or limiting the differentiation of tissues within it; in other it merely means a place where something is happening and only implies location" (Waddington, 1966/107).

heterogeneous phenomena which are not only "explained" but in fact provoked or influenced by them. So the "morphogenetic field" was introduced not only as a pure conceptual, "instrumental" means but as an *entitative* postulate.

We have now to stress that the phenomena of "individuation" (integration) were not the only observational basis for the introduction of this concept. Another important fact which intrigued some biologists (especially embryologists and those interested in the phenomena of regeneration) was phenomenal *indivisibility* of the "individuation" phenomena. If an egg divided in two parts does develop into two *complete* individuals, if a part of the "presumptive" organ region of an embryo does develop into a complete organ, as if not mutilated by the artificial division, the "morphogenetic field" has to possess a certain independence from the phenomenal structural level which is brutally manipulated by experimentalist's arbitrary procedures. (See section 6.12). Finally, it is necessary to keep in mind that the "individuation" (integration) processes (phenomena) have a rather complicated trans-temporal (trans-temporally and trans-spatially heterogeneous) structure.

"In forming a mental picture of a field we have, therefore, as a minimum to consider the three dimensions of space and the dimension of time. Even this, of course, is not enough, because we also have to consider the chemical characteristics of the different types of tissue involved. In considering a developing limb, it is not sufficient to outline the positions in space of the muscles, bones, nerves, etc., leaving out of account the fact that these tissues are different in their chemical constitution. Any precise description of a field must therefore require reference to a multidimensional space, which would have axes on which one could plot not only positions in time and the three dimensions of space, but also the concentrations of essential chemical components" (Waddington, 1966/109).[161]

9.2 "Morphogenetic field" - a descriptive or causal concept?

During the 1972 Symposium on Theoretical Biology, the question of

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[161] "An embryological field is essentially more complex in two ways [more complex than gravitational or magnetic fields]:

(a) Changes in time are among the fundamental characteristics of it and can never be omitted from its description;

(b) The material substratum' is essentially complex and cannot be described by a single parameter. An embryological field is therefore essentially a concept appropriate to the realm of discourse which deals in multidimensional spaces. Any attempt to reduce it to three or even four dimensions plus one field variable must be recognized as a drastic abstract simplification, which may perhaps be justified for certain particular purposes but must always be regarded with great caution" (Waddington, 1966/122).

the nature of the concept has provoked a discussion between R. Thom, C.H. Waddington and L. Wolpert. This discussion illustrates rather well some most important elements of the whole problem. Let us summarize the positions of the disputants.

R. Thorn, referring to a paper presented by Waddington, have said:

> [some of your paragraphs] "seem to me contradictory in spirit if not in word ... you say that the field concept has just descriptive value and no explanatory power.[162] To get a true explanation, one has to know the nature of the 'operative forces.' Only if the forces were always the same, would the field concept be a unifying paradigm; and we know that none of these conditions is fulfilled" (see Waddington [ed.], 1972/138-139).
>
> "I have very strong objections," continued Thorn," against this reductionist and anthropomorphic viewpoint. At the finest level of analysis, undoubtedly Wolpert considers, as one of the best explained morphogenetic situations, gastrulation in sea-urchin, where he can see the agents, the mesenchyme cells, with their pseudopodal activity. It never occurred to him that the problem is not solved, but just a bit displaced when you identify 'local agents': why do mesenchyme have, precisely at this time, this strange activity? Why is that this activity ceases when the two tissues have been put into contact? And so on..." (ibid., 1972/141).

In other words, Thorn criticizes Waddington's opinion that the concept of "morphogenetic field" is a solely descriptive idea, and at the same time he felt uneasy about Wolpert's attempt to attribute the properties of a "unifying paradigm" to any particular temporary and fragmentary activity observed upon different (in the cited case, cellular) levels of the body's organization.

Waddington's answer to the above criticism was this:

> "When I said that 'any concept of a "field" is essentially a descriptive convenience, not a causal explanation,' I was not expressing myself very well. There is, I suppose, in the last analysis, no distinction between a description and an explanation in terms of postulated 'operative forces'" (ibid., 1972/142).

This statement might produce an impression that Waddington is surrendering epistemologically and renouncing recognition of such a precious (to the philosopher's heart) notion as the idea of *cause.* But in fact he treats the concept of "field" as an "integrating", but not *ultimately* integrating agent.

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[162] Kühn (1971/129) quotes Weiss (Principles of Development, Holt, New York, 1939): "The field concept, is ... but an abbreviated formulation of what we have observed ... Its analytical and explanatory value is nil."

He recognizes that the concept of field is extremely complex, and that most probably many different forms of "field" should be recognized, if the description of the developmental and functional events is expected to represent faithfully the true nature of the life phenomena. He compares the great variety of "fields" to the great variety of sentences in a literary masterpiece. He claims that a "causal explanation" of how the words of a particular sentence are arranged is provided by a grammar. This, however, might again raise the objection on the part of somebody who cares more about the information communicated by the sentence as a whole than about the way in which the words have to be arranged in the sentence: the grammar seems to be only a tool, not the cause of the communicational processes. Waddington concludes: "We need to enquire what generated the field" (ibid., p. 143).

Of course, if the "fields" are numerous, different, and non-randomly "organized," the question of their integration has to be raised, too, together with the question of the origin of a concrete particular "field."

"Indivisibility" of some developmental processes, as we have said above, does not facilitate the speculative efforts to create an adequate concept of a "unifying paradigm." Let us reflect for a while upon another text which might illustrate how biologists are trying to cope with the evidence they are discovering, observing and registering.

> "It is easy to take for granted the'fact that a single transversely bisected flatworm regenerates one head. But what if the animal is also bisected longitudinally? Will each half stump now grow half a head or a whole head?" (Goss, 1969/65).

Because the experimental evidence has shown that both cases are realizable within (or by) a mutilated flatworm's body, Goss *(ibid.)* thinks that "the results of these studies have contributed much to our understanding of morphogenetic fields" (p. 65).

He tries to make the idea of the "morphogenetic field" more clear and convincing by metaphors borrowed from the physical sciences.

> "The flame of a match, for example, represents a dynamic equilibrium of burning gases which collectively maintains its shape. If a burning match is split lengthwise, the original flame is divided into two equal and complete flames of somewhat smaller size. Conversely, two matches can be brought together to produce a single flame. A magnetic field exhibits similar properties. In either case, the integrity of the field is not changed by quantitative alterations in the physical substrate from which it emanates. The so'called head field of the regenerating planarian possesses comparable attributes" (*ibid.,* p. 65).

If the flat-worm's phenotypic behaviour had not been ultimately dependent upon the *functional* mechanisms and its' regenerative processes were not following the pattern of the developmental processes, the Goss metaphor might be considered as epistemologically correct. We might even say that if the regeneration of the head in a bisected flatworm might really be considered as self-explanatory, the case of the regeneration in a longitudinally bisected body might be considered as self-explanatory too. It is rather difficult to understand why longitudinal bisection should be considered as essentially different from a transversal one.

If the flatworm's phenotype, however, is *functionally* organized, and the functional structures are *indivisible,* and on the other hand the process of regeneration of their indispensable integrity goes on with the typical developmental economy, every case of regeneration including those just quoted raises the same question. How can we explain the repetitive integration of trans-spatial and trans-temporal events which are a physical prerequisite of the restoration of the original state? During the process of bisection, was the "morphogenetic field" divided together with the body? If so, why does it tend towards the unification of parts? If not, what is its entitative nature?

9.3 The problem of the entitative nature of the "morphogenetic field"

The answer to the problem of how the postulated "fields" manage to put into an order the randomly organized (spatially and temporally) molecules or cells depends upon the entitative properties of the "field." Two physical realities are taken into consideration at present. One is a sort of electromagnetic changing field created by a special biological structure or a set of structures. Goodwin § Cohen (1969), for instance, created a model consisting of two "pacemaker cells" which produce a sort of electromagnetic field in their vicinity, and the rate of the electric impulses produced by each one of those cells might change in such a way that the produced field would be heterogeneous enough (both spatially and temporally) to provide an adequate answer to the orderly sequence of events going on in different parts of the developing body and in different time parameters (see Lewin, 1972/37).[163]

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[163] "A particularly interesting, elegant, and important mechanism for the specification of positional information based on the novel principle of wave propagation has been proposed by Goodwin and Cohen. Briefly, they suggest that two periodic signals are propagated from the reference point, the S event and the P event. The P event is propagated from the origin at a definite phase angle difference with respect to the S event, but since it is propagated more slowly the phase angle difference increases with distance from the reference point" (Wolpert, 1970/206).

The above example of the supposedly electrical signallization is really, adequate to the phenomena of self-aggregation, repair and the development in general? What about the origin of the signalling structures? What about the causal efficacy of the signals themselves? Does the heterogeneity of the above-described electrical "field" adequately explain the structural and dynamic, gradually appearing heterogeneity of living and functional bodies?

Another kind of physical reality which is a candidate for the causal agent in the "field phenomena" are specific (postulated) chemical substances produced in different parts of the body at different times of its development and diffusing into the neighborhood. They are affecting cells and tissues in a differential way according to their actual competence -- i.e., intrinsic tendency to react in a specific way. This competence would be determined by the cell's own genome (its functional state) and (which, perhaps, means the same) its whole developmental history, as well as by the different physical properties of the cell's environment. The last (chemical) theory is commonly referred to as the theory (or theories) of "gradients." A "source" of the substance is postulated together with a "sink" in which it vanishes (being, for instance, destroyed by a specific enzymatic enzyme, or enzymatic complex). Between the "source" and the "sink," a "gradient" of substance's concentration might have been detected. So the cells and tissues located between the source and the sink, which are (each one of them) in a slightly different situation, under a slightly different influence of the postulated substance, were reacting differently, and in this way more and more heterogeneous entities would develop from the originally rather homogeneous early embryonic structures.

As Waddington has put it:

> "...physicists are happy to use the concepts of the electromagnetic or the gravitational fields, but would be very hard put to it to tell us exactly what electromagnetism or gravity is. The weakness of the embryological field theory is, I now think, of a different kind. Essentially it arises because there are so many different embryological fields. There is

> only one gravitational field and we can describe how it is modified by moving things about within it. But there is a different limb field for the forelimb and for the hindlimb of the same animal and other fields for the fore-limb of different species...for this reason I think that the field concept becomes much more a way of asking questions than of answering them (1966/108).

It would take too much space and too much time to discuss in detail the advantages and shortcomings of the above-mentioned theories, so we will limit ourselves to few comments and critical remarks, which do not pretend to solve the problem of validity of those theories.

9. 4 Some critical remarks on the concept of the "morphogenetic field"

At the present moment the speculative elaboration of the concept of field usually starts with a rather arbitrary selection of "pattern." Strikingly enough, the "patterns" which attract the attention of the "morphogenetic field" theorists constitute as a rule a specific kind of morphological phenomena. They are all characterized by their geometrically regular features, not by functional aspects of their structure. Any pattern which resembles more closely some well-known and rather simple geometrical figures, such as spirals, stars, concentric circles, parallel rows and so on are considered as more "patterned" than other morphological elements, or aspects of the living body (see, for instance, Thorn, 1970/89ff.).

In a way, like Mendel, who selected some physiologically (functionally or developmentally) secondary phenomena for his genetic analysis, in a similar manner the "morphogenetic field" theorists select those aspects of the patterns recognizable in a living organism which offer an easier substrate for further geometrical or mathematical processing.

This sort of procedure might be fruitful, but there is a danger involved in it. From the history of brain anatomy we know fairly well how the repetitive pattern of some brain surface convolutions determined the speculative "functional" regionalization of this organ. Later, physiological analysis discovered that spatial properties of the anatomical details, however intriguing they may be, do not always follow the functional, dynamic pattern of relationships, which is the one which counts, in the last analysis. A scientist, of course, has to look for an easier way of discovering or describing the reality, but this methodological and legitimate principle should be kept in balance with the principle of relevance of the evidence observed. During our previous analysis we distinguished between developmental, adaptive, functional and individualizing aspects of the bodily

patterns (both static and dynamic). Now, some patterns are obviously relevant both in the functional and developmental sense, some, however, are relevant in the "individualizing" sense, but not necessarily functional, or developmental one.

Because of the above selective description of the developmental, functional, regenerative phenomena, the models of the "field phenomena" seldom, if ever, resemble the description of the really operative mechanisms discovered by physiologists or embryologists. The selective, abstract treatment of the object of study leads to relatively simple concepts of bodily structure. These concepts are easily translatable into mathematical functions and, later on, these functions serve as a model for explanatory hypotheses concerning the causal entitative nature of the somewhat artificially created concept of a given field. If the physiological mechanism was reduced by abstract and arbitrary selective description to a rather simple geometrical form, the explanation of the origin of this form is of course considerably simplified too.

The development of a vertebrate limb may be explained by the simple concentration gradient of a more or less homogenized molecular signal, or an electrical oscillator, on the condition that the morphology of the limb was reduced earlier to the "pattern" of a triangle, for instance. Similarly, the structural "pattern" of Hydra's body may be so simplified that the interference of a couple of molecular or electrical signals may be sufficient to represent the full "complexity" of the "pattern." But the relationship between the real living structure and the concept of "pattern" abstracted from this structure is to be analyzed before the validity of the explanation in terms of gradients and pacemakers could be seriously taken into consideration.

The explanatory validity of the "gradients" and "oscillators" might be verified by discussion of the experiments on self-aggregation.

Let us reflect upon the observations on the mechanically disrupted body of *Hydra attenuata.*

> "Suspensions of hydra cells were produced by mechanical disruption of hydra-tissue in a modified cell culture medium ...Between 70% and 80% of the cells are interstitial cells [I-cells], nemotoblasts, nerve cells, and gland cells all of which occur almost exclusively as single cells. The remaining 20%-30% are epithelial cells [epithelio-muscular calls of ectoderm and endoderm] of which one-third are single, one-third in clusters of two to four cells and one-third in clusters of five to fifteen cells.

> "Reaggregation of hydra cells occurs spontaneously in dense cell suspensions — if tissue disruption was too severe epithelial cells were selectively destroyed and no aggregates formed...Aggregates must contain a minimum number of cells...The 33,000 epithelial cells in the final regenerate cannot be derived from a minor fraction of the original cell suspension...because no significant epithelial cell mitosis[which is an observational sign of the cell multiplication - PL] occurred during this period.
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> "The initially irregular cell mass forms a firm aggregate. ..within 6h .... After 20-30 h the aggregate develops into a hollow sphere...By 40-48 h tentacle buds begin to appear—After about 2.5-3 days hypostomes appear...At 5-6 days the regenerate is able to feed on *Artemia.* Eventually the hypostomes divide up the tissue and several normal animals develop. Later the animals are capable of budding " (Gierer et al. 1972/98).

The above example constitutes one of innumerable experiments of self-aggregation potential of tissues, organs or whole bodies disrupted by experimental procedures. They all provide a persuasive illustration of the relative independence of the structurally integrating agency from the structural state of the body. An adequate causal explanation of all these phenomena cannot be based upon a structural spatial framework, simply because this framework was destroyed during the experiment.

Summing up the above sketchy and fragmentary remarks upon the idea of "morphogenetic field," we may say that the idea conveys three different concepts:

a) It refers to the phenomena of the "life cycle" especially in its developmental, adaptive and regenerative aspects. In this sense the idea of the "morphogenetic field" is reducible to the redescription of the whole, or of part of the "life cycle."

b) It may refer to the highly abstract notion of structural "pattern" recognizable at one stage or another of the essentially indivisible dynamic phenomenon of the "life cycle." The biological relevance of the abstract "patterns" considered as "classical" examples of "morphogenetic field" manifestation has yet to be verified.

c) It may refer to concentration gradient, an electrical oscillating "field" or other physical more or less heterogeneous physical parameter postulated or actually measured within the living body. This parameter (its temporal and spatial organization) is expected to constitute the adequate system of signals or triggers which coordinate

and integrate the different fate of differentiating cells within the developing organism.[164]

As a whole, the idea of the "morphogenetic field" remains rather unclear. Berill states that "Morphogenetic fields and biological-field phenomena, which are real though enigmatic, may have an electrochemical basis" (1971/359). Apart from the methodologically questionable way in which the "field" phenomena are described and abstracted from the observational evidence, another serious objection against it may be drawn from the above-described experiments. If Wolpert et al (1972), for instance, distinguishes between the "source" and the "sink," if Goodwin and Cohen (1969) postulate the structurally organizing mechanism based upon the idea of spatially distributed electrical pacemakers, all these postulatory mechanisms fall down because the proposed "organizing" elements become randomized together with the rest of the disaggregated structures.

It is impossible to exclude the eventual role of the postulated mechanisms upon this or any other stage of the complex dynamics of the mul-ticellular "life cycle." In fact, some of the life processes may operate according to the scheme of "positional" information, or according to the scheme of "oscillator" model proposed by Goodwin and Cohen (1969). But the above mechanisms do not seem to be adequate in explaining the basic phenomena of the "life cycle's" integration, and the entitative elements constituting them could hardly be considered as an adequate constraining agency ultimately responsible for the trans-spatially and trans-temporally integrated phenomena of development, adaptation and repair.[165]

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[164] "A field concept in the above sense could be used in connection with any developing system. In practice, the temptation to use it arises only in connection with systems which exhibit some general integration of the future developmental pathways followed by the different subregions within the whole; for systems, that is to say, which exhibit some degree of 'regulation.' Any such regulative properties can be expressed by specifying some 'normal' developmental pathway within a multidimensional space and describing the manner in which it acts as an attractor for neighboring'pathways. A region of phase space characterized by an attractor time trajectory has been called a chreod. A developmental field is essentially a chreod, whereas electromagnetic and stationary gravitational fields are not"(Waddington, 1966/123).

[165] "How strong is the field character? One of the most important characteristics of a field or a chreod is that there is a trajectory of 'normal development' which acts as an attractor for neighboring trajectories, so that 'regulation' takes place back toward normality"...(Waddington, 1966/115). The "trajectory of normal development" is conceived here as a sort of active, causal agent. Still the concept of this "trajectory" is essentially trans-temporal. It could not be reduced to a coexistent structure.

CONCLUDING REMARKS

Man, in the state of full consciousness, does not register passively phenomena which provoke sensations on the level of his sense organs. He manifests a need for understanding. He is able to select puzzling elements of reality and believes in his capacity for guessing, inferring, or at least postulating a correct explanation of mystifying aspects of the natural world in which he is immersed and of which he himself is a part. The distinction between the "question-raising" element of his fragmentary knowledge of the universe and this insight which legitimately satisfies his inquisitive mind constitutes the crucial epistemological polarization within the whole bulk of data collected during scientific research. At the beginning of our study we decided to analyze the "question-raising" element of the science of heredity (sections 1.5 and 1.6). This analysis has led us to the following results:

a) We have recognized that the "life cycle" constitutes the elementary, non-arbitrary unit of life phenomena (section 3.3).

b) We have realized that the strict repetitivity of the "life cycles" (within a given species or a given race) provokes the question: "What is ultimately responsible for the essentially repetitive structural and dynamic pattern (the phenotype) observed within a single "life cycle"? (sections 3.21 and 3.22).

c) We have noted that the above-mentioned pattern in its "basic," "adaptive" and "individualizing" aspects is of epigenetic nature.

This fact of the *de novo* formation of bodily structures is commonly referred to as the "self-reproduction" of living beings. Repetitive epigenesis raises the question of the non-random constraints which are capable of organizing random matter and random energy of the surroundings into the highly ordered pattern of the "life cycle."

The next step of our study consisted of investigating the extent of integration within the epigenetic processes of the "life cycle." We have undertaken the analysis of the functional and the developmental events. The main steps of this analysis may be summarized as follows:

(d) We have shown that a functional event consists of an irreversible transfer of energy between two different material entities, and that this transfer is characterized by the utmost economy, i.e., the amount of free energy lost within the functional system is minimal for a given

set of environmental parameters (section 4.8).

(e) The above has helped us to realize that the functional event constitutes a purely physico-chemical form of dynamism and that the main speculative problem it raises consists not of the question "how does it work?" but in the question "How do the functional structures originate?" The empirically proved repetitivity of the functional events, the directly observable repair of the functional systems and the *de novo* formation of the functional structures, all this seemed to postulate a physically adequate developmental activity.[166] (Sections 3.17 and 4.13).

(f) Further on we investigated the minimal set of requirements necessary for the origin of a functional system. This has revealed an intrinsically heterogeneous four-dimensional structure of the developmental process, and, what is more important, it has put forward the problem of the intrinsic integration within this developmental process (section 5.7).

(g) We have recognized two forms of this integration, which seem to be irreducible one to another. One is the integration of the sequential epigenetic steps leading to the gradual change of the simpler molecules into the more complex, functional ones (epigenetic integration). The second form of integration consists of the integration between the different epigenetic paths producing different but intrinsically necessary parts of the function system (section 5.8).

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[166] Riggs (1967/357ff.) tried to find an abstract general set of conditions which are minimal for a system which shows the properties of the feedback relationship. In a way he aimed at establishing an abstract Smallest Sufficient Condition (see Broad, C.D., 1968, Induction, Probability and Causation, Reidel Publishing Co.) for the feedback relationship. This abstract Smallest Sufficient Condition being applicable to any feedback structure equalled an Absolutely Necessary Condition of this structure. Riggs succeeded in showing that two different physically independent processes coupled together into an interdependent "loop" characterize univocally these systems which may be legitimately called *feedback* relationship.

The essentially same method of analysis was used in our discussion of functional events and developmental processes. .And in both cases we have formulated what Broad might call "condition of e which has zero dispensability" *(ibid.*, p. 178). In our case, e represented functional event or developmental process.

Broad's Co-operative Bond (relation S) and his Consecutive Bond (relation R) seem to represent the ideas closely related to our concept of the trans-temporal and trans-spatial constraints.

The above results have shown an irreducible distinction between the functional events and the developmental processes. They have also shown that the "life cycle" structures, upon any arbitrarily selected stage, are never describable in terms of a fully functional system. In other words, any arbitrarily selected stage of the "life cycle" is composed of structures which "function," of structures which "develop" and structures which just pass from the random surroundings into the non-randomly organized sphere of living entity. This logically inevitable conclusion excludes the possibility of considering the living organism as a sort of intricate, complex machinery intrinsically determined to operate in a non-random manner.

In the further part of our essay we analyzed the meaning of the integrating causal agency postulated by the genetic theory. It was shown that the idea of this agency, commonly referred to as the" genome [genotype), is composed of several rather distinct postulates. Three of them summarize the active properties of this agency, and these properties are essentially identical with the idea of trans-spatial and trans-temporal constraints recognized in the concept of the developmental process (sections 6.5; 6.6 and 6.8). Two other postulates of the genome, the Postulate of Complexity and the Postulate of Chemical Nature, refer to the entitative aspect of the genome.

We analyzed the theory which identifies the genome's agency with the DNA molecule and the theory which identifies it with more complex set of chemical entities appearing during the "life cycle" (the phenotype), We showed that:

(h) Although the structural properties of the DNA molecule do explain to some extent the repetitivity of the polypeptide structures, they are not sufficient either structurally or dynamically to provide the adequate answer for the productions of polypeptides alone, not to mention other molecular components of living bodies (section 7.10).

(i) The further development of the above theory in the form of the Monod and Jacob model of gene regulation (TTM) and the theory of self-aggregation (TSA) were shown to constitute fragmentary mechanisms, operating within a limited range of the "life cycle" phenomena. They are inadequate to constitute the integrative dynamic element postulated by the "question-raising" phenomena of the "life cycle." These theories (models) in fact seem to re-describe or to postulate some or another phenotypic element, and, even if confirmed by further experimental data, should be treated as the "re-description" of the main "question-raising"element of the phenotype rather than its "explanation"(sections 8.4 and 8.5).

(j) The theory of "morphogenetic fields" developed upon the basis of evidence concerning the developmental phenomena of multicellular "life cycles" constitutes a highly abstract, partially arbitrary, and principally descriptive conceptual framework. The dynamic, causal postulates such as the "theory of gradients," for instance, which have been developed in the context of the theory of "morphogenetic fields" although they may also prove to be correct in some particular instances, fail, however, to fulfill the postulates of genome conceived as a supreme integrating, developmental agency of the phenotypic "life cycle" (section 9.4).

Although (mainly because of the technical difficulties) the study of biochemical reactions is still relying upon the model of random, thermal collisions, modern molecular biology is quite aware of the fact that the dynamic events underlying the structural developmental changes observed during the "life cycle" are not only based upon the non-random dynamism, but even exclude the random dynamism in principle (see, for instance, Green and Goldberger, 1967/81-3, and Morowitz, 1970/135). This does not mean that the random, thermal movements are not observed or not operating in the organisms. It means only that these movements cannot represent the essential form of dynamism which is capable of giving the correct answer for the main epigenetic, adaptive, developmental, functional processes characterizing the "life cycle" phenomena.

The main "question-raising" problem of the "life cycle" therefore remains unsolved. The only adequate explanation in sight seems to imply a dynamic, active agent, integrating heterogeneous events in the spatially and temporally multidimensional reality of the "life cycle." The agency seems to be necessarily stable, i.e., independent of the phenotypic influences. Its dynamic aspect is represented most properly by the notion of constraints which do not enrich the dynamism characteristic of the inorganic matter but which do limit this dynamism, changing it from the random into the ordered one. The nature of this agent remains obscure.

One may think that the vitalist's ideas exaggerating the dualism of the concept of the living being are out of consideration, but the obvious phenomenal

integration of the life cycle inevitably calls for some new entitative concepts which almost certainly will prove to be absolutely irreducible to the entitative concepts sufficient for an adequate explanation of the inanimate world (see Polanyi, 1968).

The crucial problem of the genome, conceived as a supreme agency integrating the "life cycle's" dynamism is essentially entitative. We are close to understanding the effects of its integrative activity, but we are far away from an adequate conceptual representation of its nature.

Using Herskowitz's metaphor, we may compare the "life cycle" to a factory producing automobiles. Let us imagine that humans who control different processes of the whole production are invisible. Let us imagine that we are observing the movements of the raw material, the activity of different machines preparing parts of the engine, of the chassis, of the instrument panel, etc. Let us observe how the parts move into their proper place until the fully functional structure of a car is ready to leave the factory on its own.

However detailed the whole description of these events might have been, would it be sufficient to provide the correct and adequate causal explanation of how the car is produced? The presence of humans, although, as we have assumed, they were invisible, should be postulated. We might not be able to state whether they are biped or quadruped, we might be unable to guess whether they breathe or blink, but the reconstruction of the "missing" steps under the direct control of the "invisible" agency might quite properly be effected.

This image if applied to the causal problem of the "life cycle" phenomena resembles generally the idea represented by Maxwell's demon.

But we might try to conceive the same factory producing cars as an integrated, living organism. We might claim that the machines, the parts under preparation and even the raw material which is "sucked" from outside constitutes a sort of a dynamic whole, intrinsically determined to produce functional structures of cars.

If this last concept were correct, the dichotomy between the "phenotypic" aspect and the "genotypic" aspect of the organism would vanish altogether. We would have to do with a strange automaton which goes on continuously producing repetitively new automatons of the same kind, and the only causal factor in this repetitive, trans-temperally heterogeneous cycle would be the chemical structure of any arbitrarily selected stage of the cycle, plus

the randomly organized matter and energy of its surroundings.

This structure, however, as we have stressed before, is always only partially functional. Even if it were totally functional, i.e., self-explanatory in its dynamism, its origin would remain unexplained. *A fortiori* the structural transformations, the whole dynamism of the "life cycle" remains mystifying if it is only partially functional.

We have to ask ourselves whether the monistic axiom most evidently implied by the Postulate of Chemical Nature of the Genome is really conciliable with the seemingly necessary first three postulates concerning the activity of the genome (Autocatalysis, Heterocatalysis and Stability). The prospects of an affirmative answer seem rather faint.

The meaning of the dichotomy between the phenotype and the genotype constitutes most obviously one of the crucial problems of contemporary biology. Its implications and applications can be traced in every domain of biological research, both empirical and theoretical. However, the empirical data are dazedly complex and heterogeneous. The speculative attempts to abstract, a more essential and relevant aspect of them are only partially successful, principally because the notion of "relevance" still remains rather vague and imprecise. The construction of theoretical models and hypotheses is determined (or at least closely linked) with most basic metaphysical beliefs and epistemological convictions of the contemporary period of man's history. All this creates serious restrictions,and limitations for theoretical elaboration of the observational data. It would be unreasonable to take for granted that all these restrictions and limitations are objectively valid and that they should be respected.[167]

The more subtle experimental and observational techniques that are gradually being introduced, the more manifestly deficient is the purely statistical estimation of causal relationships operating within the living body, and the more correct our ideas of actual processes characterizing the "life cycle" become. In this sense, the purely statistical description so strongly criticized by Lorentz (1973/lff.) is already replaced to a great extent by the detailed representations of functional and developmental structures and processes. But this higher (in comparison with the purely statistical) level of

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[167] "The synthesis of molecular biology into an integrative physiology of whole organisms eludes us. We lack a philosophy of hierarchical systems adequate to our task of understanding the behavior and the organization of whole organisms, and we are left with a persistent dichotomy between reductionism and holism" (Yates et al, 1972/111).

knowledge does not constitute the ultimate level of explanation. It calls for an integrative explanation. This ultimate aim o£ biological research is still represented by the idea of the genome agency. Berill summarizing the problems raised by the multicellular "life cycle" phenomena asks:

> "What are the guidelines that organize, or enable cell populations to self-organize, into the shape and structure, dynamically maintained, of the organisms as a whole?" (1971/514). The lack of the integrative explanation upon the level of the unicellular "life cycles" does not seem to be less obvious " — the new information serves as much to raise new questions as to clarify old ones" *(ibid.* /193).

One thing seems obvious enough. Upon the level of description and experimentation, the reductionist and monist program is quite fertile. It provides us with sound, repetitive, verifiable evidence. The main controversy starts upon the level of the speculative elaboration of data collected by empiricists.[168] We may safely conclude that a deeper insight into the nature of generalizations and metaphysical assumptions operating upon the speculative level of biology seems necessary. The actual forms of exercising the empirical study may provide us with many important hints concerning the real nature of the speculative process involved in scientific discovery. This in turn may lead to the revision of some anti-metaphysical taboos which intimidate a free and unprejudiced discussion of the logically correct hypotheses and theories leading to the more coherent and more illuminating insight into the true nature of life phenomena and the causality which underlies these phenomena.

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[168] "However basic it is to know the properties of bricks, mortar, steel, wood, glass and soil in building a house, that knowledge alone can never tell how to get architecture into that pile of stuff. The knowledge of the chemical and physico-chemical properties of isolated collagen or mucopolysaccharides alone cannot define the difference between a random callus and a well-formed piece of skeleton. Indeed the knowledge of how the 'genetic code' -- sequences of nucleic acid residues -- is transcribed and translated into a repertory of proteins, including the enzymatic ones, cannot of itself explain how to get from a random bag of proteins to the organized system of subcellu-lar, cellular and intercellular structures which we discern as form and which distinguish orderly from chaotic activity. "This problem of 'organization' must not be allowdd to remain a mystical symbol; it must be subjected to rigorous scientific investigation and description, even though it may not be resolvable to purely reductionist term"... (Weiss, P., 1965/256).

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