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Alfred Kühn, his work and his contribution to molecular biology

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Among the developmental biologists of this century Alfred Kühn is an outstanding personality. Of greatest impact are his studies on the action of genes in development that made him a pioneer of the "one gene-one enzyme" hypothesis. This aspect will be in the center of the following report. However, it would be unjustified in view of his universality and broad influence not to mention his other scientific interests comprising an astonishing variety of themes and objects. Much of this work can be traced back to his early period of scientific activity in Freiburg.

Kühn himself published only a short biographical account on his scientific career until 1937 (Kühn, 1959). He was born on April 22nd, 1885 in Baden Baden (South West Germany), attended the gymnasium in Freiburg im Breisgau and began studies of science at the university there.

Of greatest influence were the both, Prof. August Weismann, zoologist and evolutionist, and the physiologist Johann von Kries. It was the latter who suggested investigations on sensory physiology, e.g. on the function of the labyrinth of reptiles (Kühn and Trendelenburg, 1908) and on statocysts of crustacea (Kühn, 1914). Such studies culminated in a survey on "The spatial orientation of animals" (Kühn, 1919) which contributed significantly to a classification of notions and a deeper understanding of the underlying behavior. It directed the emerging "Verhaltensphysiologie" for many years. Kühn also contributed innovative and important papers on color vision of insects (partially in collaboration with the physicist Pohl; Kühn and Pohl, 1921) and cephalopods. Last but not least we owe Kühn the first "Manual of experiments in animal physiology" written by a zoologist (Kühn, 1917).

Of deepest influence on the young student was August Weismann. His encyclopedic knowledge and ".. the most serious and lifelong dedication to a great problem, namely the formation of the theory which should solve the questions of inheritance and evolution" (Kühn 1959) were of great impact for Kühn. Weismann's research projects and objects laid the foundation for his interests in developmental physiology.

After his promotion (1908) Kühn became second assistant of Weismann. Following his habilitation (1910) he worked as "Privatdozent" and subsequently became "a.o. Professor" (associate professor) at the Zoological Institute in Freiburg. Research periods in Naples and Heidelberg helped to enlarge his experiences in a variety of projects. During World War I he was a medical orderly (1915-1918). The following two years he cooperated with the famous embryologist Karl Heider at the Zoological Institute in Berlin. In 1920, Kühn received the call to become full professor in Göttingen. During the subsequent 17 years full of activities he transformed the institute to a place for modern research and teaching. In this time the foundations for his success in genetics and developmental biology were laid. Göttingen was a unique place at that time. The collaboration of outstanding scientists and mathematicians and the stimulating mutual exchanges created the background for fruitful research. Especially successful was the collaboration with the botanist Fritz von Wettstein (during the period 1925-1931). With him, Kühn shared many interests in research and teaching. It was unique at that time in Germany that lectures in the same topics (genetics, developmental biology) were given alternatively from two lecturers as fundamentals of a "General Biology".

Increasing pressure of the NSDAP (Nazi-Party) after the "Machtübernahme" (Grossbach 1988) prompted Kühn to leave the University of Göttingen. Just at that time the "Kaiser-Wilhelm-Gesellschaft" could offer him the position of a second director of the "Kaiser-Wilhelm-Institut für Biologie" at Berlin-Dahlem. He took over the position of Richard Goldschmidt who emigrated in 1936 to the USA. This change enabled Kühn to continue and intensify his research work.

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As a consequence of the war, the translocation of the institute in 1943 to Hechingen (South West Germany) and the loss of important coworkers reduced the scientific activities for a few years. They could be reassumed only after the new "Max-Planck-Institut fur Biologie" in Tübingen was created and ready for occupancy in 1951. In 1958 Kühn retired from his position as managing director but continued scientific research until shortly before his death on November 22nd, 1968. For five years (1945-1950) he was also the head of the Zoological Institute at the University of Tübingen.

At that time he was once again engaged in teaching demonstrating his impressing talent as an academic teacher. His presentations were clear and impressive – always without manuscript even in two hour lectures – vivid, meaningful and eloquent, until his old age. Better than any textbook could do, he impressed his students with his carefully selected examples and his illustrations in form of large format lantern slides.

Many honors were conferred to him: membership in several domestic and foreign academies, scientific prizes and finally the highly selected award of the "Orden Pour le Mérite der Friedensklasse für Künste und Wissenschaften" in 1964.

Of long lasting influence, first of all in the German speaking scientific community, were the textbooks of Kühn. They reflect his universal spirit, his power as a lecturer who concentrated on the essential, but also his didactic and artistic gifts. His "Grundriss der allgemeinen Zoologie" (Basics of General Zoology) was published in numerous editions since 1922. This book influenced generations of students in Biology and Medicine. Even the new edition revised by R. Wehner and W. Gehring uses Kühn's schematic drawings of the "Baupläne" of animals. The several editions of his "Grundriss der Vererbungslehre" (since 1934) enables one to follow over the decades the increasing knowledge in genetics to which he contributed to considerable extent. The last great book of Kühn "Vorlesungen über Entwicklungsphysiologie" (1955, 1965) is unique in the thoughtful analysis of the problems of developmental biology. The basic questions of development, morphogenesis, and differentiation are presented in this book in a masterful way, even if molecular biology has greatly deepened our insight into the processes of development since then. Kühn showed the way of future research when he wrote: "For the time being we can only describe the <use> of one of these principles and their interaction. In the future the conditions for the initiation of certain reactions and their termination eventually should be traced to physico-chemical steps – a far distant goal, indeed! " We are much closer to this goal in our days.

Another important facet in Kühn's personality is his interest in the history of science. His studies of certain periods of scientific development show his inclination to be aware of the roots of scientific cognition and to understand their historical and human dependencies. Kühn published numerous biographical sketches, e.g. on K.E. von Baer, Mendel, Weismann, Boveri, Spemann, von Wettstein, Goldschmidt, but also detailed studies such as "Goethe und die Naturforschung" (Kühn, 1933), "Biologie der Romantik" (Kühn, 1948) and "Anton Dohrn und die Zoologie seiner Zeit" (Kühn, 1950), all of them comprehensive surveys.

Let us go back to Kühn's experimental work. During his first years in Freiburg, Kühn worked not only on physiological studies. Under the influence of Weismann he pursued mainly two problems. In Weismann's concept of heredity and the realization of hereditary information the "Keimplasma" presented the continuity throughout the sequence of generations. In this context Kühn analyzed the development of reproductive cells ("Keimbahn") in parthenogenetic crustacea and the obviously determinative development of the embryo of *Polyphemus*.

Another topic was his extensive research on Hydrozoa conducted in the much appreciated Stazione Zoologica in Naples. Starting from studies on the branching patterns of developing Hydroids it culminated in a voluminous presentation of the ontogeny and the phylogenetic relationships among Hydrozoa (Kühn, 1913). Cytological investigations on amoebae contributed to a deeper understanding of the interconnections between nuclear and cytoplasmatic division.

Numerous and diverse contributions to animal morphology followed well into the thirties. Among them were publications on the morphology of sensory and nematocyst organs in Hydrozoa (Kühn 1914-1016), the rudimentary "Morphologie der Tiere in Bildern" (2 volumes, Kühn, 1921, 1926), and an article on Hydrozoa in the "Handwörterbuch der Naturwissenschaften" (Kühn, 1932). These publications show Kühn's talent for careful observation and artistic presentation. He himself in private talk spoke sometimes of being an "eye-minded person". He was fascinated by studying the great diversity of animal forms and structures and their development in ontogeny and evolution. Again and again they stimulated him to ask causal questions.

Weismann's experiments on temperature modifications of the wing patterns of lepidoptera had a lasting influence on Kühn's subsequent activities. Weismann treated these modifications from the standpoint of an evolutionist. For example, he considered the "winterform" of the dimorphic butterfly *Araschnia levana* as being the phylogenetic older one having evolved in the last glacial period. Kühn's approach was that of a developmental biologist: The modifications of the wing pattern caused by changing temperature offered him the opportunity for an experimental analysis of a relatively simple, two-dimensional color pattern. In collaboration with Karl Henke, his coworker for many years (who became his successor in Göttingen) Kühn pursued systematically the influence of external and genetic factors on the wing development. For this purpose they used a carefully selected species, the flour moth *Ephestia kuehniella*. (This moth was not named in honor of Alfred Kühn but of a previous director of the Agricultural Institute at the University of Halle who was first asked to determine this pest).

Kühn and Henke looked for mutants with altered wing patterns and simultaneously they analyzed corresponding phenocopies (Kühn and Henke, 1929, 1932, 1936). Thus, the genes intervening in the process of pattern formation eventually became comprehensible. This widely used method is enormously successful in the studies of genetic embryology still today (Nüsslein-Volhard and Wieschaus, 1980). The lepidopteran wing proved to be a very promising system because each scale as a product of a single cell within the wing epithelium tells its developmental history. Its particular size, shape and form reflects distinct local conditions acting during the time of its commitment or differentiation. Based on these advantages Kühn and Henke studied factors of wing development from the level of the whole pattern and his subareas to that of the single scale. An instructive example is the action of the gene *Sy* of *Ephestia* which is responsible for drawing closer the anterior and the posterior wing band. This effect also can brought about by temperature changes or local heating during a sensitive period. Thereby the inhibition of a spreading determinative factor was conceivable.

In a similar way several mutants were selected and used as useful probes for otherwise hardly approachable steps in development. Moreover, Kühn became increasingly engaged in the second aspect of gene action, namely to find out how genes immediately control the traits and processes that depend from them. In 1929 a red eyed mutant with the recessive gene *a* was found in *Ephestia* which opened the door to tackle the last-mentioned question.

Ernst Caspari stated in his dissertation (1933) which he had done with Kühn: "Up to now one has not tried to solve the question of the mode of action of genes applying the method of microsurgery so much in use in developmental biology". He employed it and transplanted testes between larvae of the black-eyed wildtype and the mutant in both directions. He found that the light testes of the mutant *a/a* took the dark-violet color of the wildtype testes, whereas a^+/a^+ (Caspari wrote *A/A*) testes in the a/a host developed the dark color inducing also the host eyes to become dark. Since the transplanted organs had mostly not been in direct contact with host tissue the influence had to be transmitted humorally via the hemolymph. Caspari's conclusion was therefore: ".. an *A*- testis liberates a substance with the ability to trigger pigment production in testes and eye cells which lack an *a* gene".

This was the first time that the action of a gene by transmission of a soluble factor was demonstrated in an experimental organ transfer. A new door to developmental genetics was thus opened. Pigment production was easy to recognize and could be analyzed chemically, in contrast to other morphological differentiations brought about by genes. Kühn and his group (including the assistants Ernst Caspari, Ernst Plagge, Hans Piepho and later on Erich Becker as biochemist) set the stage for a prosperous work. Already two years later Kühn, Caspari and Plagge (1935) presented a considerably enlarged concept. It included all phenotypic expressions of the a^+ gene known at that time: pigmentation of eyes, brain, epithelium of the testes, larval epidermis and eyes (stemmata), and it took into account the influence of other transplanted organs and of the different developmental stages (Fig. 2). The authors also were able to demonstrate a maternal effect: larvae of the genotype *a/a,* the offspring of heterozygous mothers after backcross, exhibit a wildtype-like pigmentation of the stemmata and epidermis, which gradually fades. Kühn and his coworkers concluded "..that a substance, produced by *A*-tissues is transmitted to the egg via the hemolymph".

Concerning the nature of this product they discussed 3 possibilities: 1) a general precondition for pigmentation like pH or other characteristics of the milieu; 2) ".. material necessary for the proper formation of pigment, e.g. a chromogen"; or 3) a stimulating or otherwise effective substance which triggers the formation of a certain process like a hormone.

Influenced as they were at that time by the observed maternal effect Kühn's group considered the 3rd alternative as the most plausible one. They could not imagine that the amount of a substance enclosed in an egg might support pigmentation in the

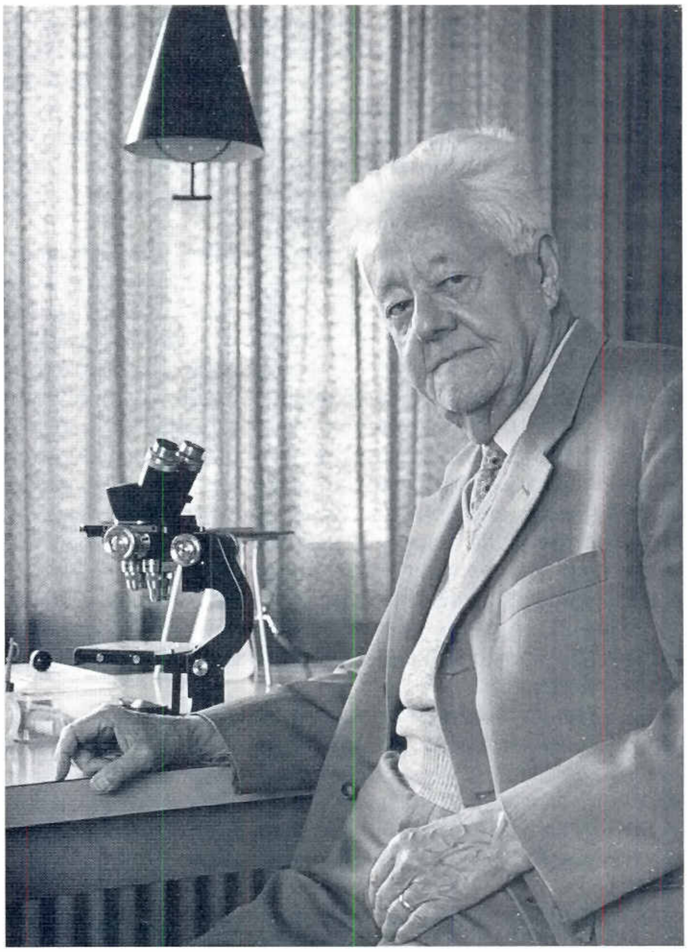

Fig. 1. Alfred Kühn (1885-1968).

larva over weeks. This misinterpretation also prevailed in contemporary publications in the United States for several years, until the involved gene-"hormone" was found to be a precursor of the pigment.

Approximately at the same time the American geneticist George W. Beadle and the French embryologist Boris Ephrussi published comparable results on *Drosophila melanogaster* which they obtained in cooperation initiated shortly before. Beadle and Ephrussi transplanted imaginal eye disks between larvae of the wildtype and of different eye color mutants. Fortunately they could rely on a much greater collection of mutants than that which was available for *Ephestia.* Surprisingly Kühn never used mutagens to enlarge his stocks of suitable mutants. He only offered prizes for newly discovered spontaneous mutants.

In *Drosophila* two mutations proved to be non-autonomous and useful for future work: *v (=vermilion)* and *cn (=cinnabar).* Beadle and Ephrussi came to the same conclusion than the group in Göttingen, namely that a gene defect in the mutant *v* is responsible for the production of a diffusible substance which is necessary for pigment formation. They concluded furthermore, that ".. *v* and *cn* host-implant influences are genetically – and presumably chemically – closely related" (Beadle and Ephrussi

1935). They were inspired by Sturtevant to perform these experiments (Beadle, 1951). It was Sturtevant who formerly has found that in v^+/v mosaics the eye of the *v*-half is colored like wildtype and, therefore, that the v^+-gene is expressed non-autonomous (Sturtevant 1920, 1932). Caspari also knew these results. That Caspari's paper which was quoted by Beadle and Ephrussi but not discussed in detail was of influence for their experiments can at least be assumed (Harwood, 1993) .

During the next years both groups worked very efficiently. Between 1935 and 1941 Beadle and his coworkers published over 30, Kühn's group 22 papers in this field. Directed by the same concept and using similar methods they both demonstrated that the problem was ready for being solved. Eventually their research diverged but the most important goal was to find the primary action of genes. Beadle and coworkers were able to demonstrate that the substances dependent from the gene *v* and *cn* are products of subsequent gene activities and, thus, links of a chain (Beadle and Ephrussi, 1937). Furthermore they showed the homology of the respective genes with corresponding ones of the wasp *Habrobracon* (Beadle *et al.,* 1938). In turn Becker and Plagge (1937; Plagge and Becker, 1938) demonstrated the homology of the genes $A{=}a^+$ of *Ephestia* and v^+ of *Drosophila,* respectively. They concluded, therefore, that their gene products should be identical.

Both groups continued the search for the chemical composition of these gene products. Important steps in this approach were the isolation of active extracts from both objects (Becker 1937; Khouvine and Ephrussi 1937), the modification of the diet of *Drosophila* as a means for influencing the pigment formation, and the proof of a bacterial synthesis of the v^+-product (Tatum, 1939).

Cooperation with experienced biochemists (A. Butenandt and E.L. Tatum respectively) culminated in the expected breakthrough: Beadle and Tatum presented evidence for the v^+-substance being kynurenine, the derivative of tryptophan (1940, quoted after Harwood 1993) . But they had to recognize that in the meantime Butenandt, Weidel and Becker (1940) had come to the same result. It is not astonishing that such a race provoked irritations (Harwood, 1993) . Both groups acted at the research front in pursuit of a highly actual problem. Besides, both groups were effectively supported by the Rockefeller Foundation in the frame of a project initiated by Warren Weaver for promoting "physiological genetics". Kühn (1959) remarked with gratitude that he would not have been able to carry out his investigations in such a striking way without this support.

The efforts of both groups culminated in the influential concept of the "one gene – one enzyme" hypothesis, as formulated by Beadle and Tatum (1941): "Each gene controls the reproduction, function, and specificity of a particular enzyme". Kühn (1941) became not aware of this statement when he wrote simultaneously: "..with the genes $a^+= v^+$ enzymes are made available which catalyze these processes". Beadle presented a more differentiated formulation because in the meantime he turned to a new object, the mold *Neurospora crassa.* The production and isolation of numerous metabolic mutants gave him and his coworkers the possibility to verify manyfold the one gene-one enzyme concept, even in its later extension "one gene-one protein" (Beadle 1946). Thereby the foundation of molecular biology was laid . The elucidation of DNA structure and protein synthesis and the deciphering of the genetic code denote further steps along this way. The work of Beadle, Tatum and Lederberg was honored in 1958 with the Nobel prize.

The basic idea of a connection between genes and chemical substances or processes, however, has been expressed much earlier (e.g. by Garrod, 1909; Gross, 1914; Onslow, 1923; Goldschmidt, 1927; Haldane, 1938; quoted after Beadle 1946, 1951) . But the direct and continuing tackling of the problem was initiated by the experimental approach using the mutants of *Ephestia* and *Drosophila* defective in pigment synthesis. Undoubtedly Kühn took the first decisive step.

Kühn was always open-minded towards suggestions and proposals of competent colleagues. Exceptionally productive was his collaboration with Adolf Butenandt, the later Nobel laureate. It started in Göttingen and was continued in Berlin-Dahlem and Tübingen and resulted in two main streams of research:

1) Kynurenine and 3-hydroxy-kynurenine (Butenandt *et al.,* 1949) were found to be intermediates of ommochrome synthesis. Biochemists were attracted in particular by the analysis of this new class of pigments. Again Becker (1939, 1942) was the first who named and characterized ommochromes. Butenandt and his coworkers were able to elucidate the constitution of several ommochromes and to characterize them as phenoxazones (Butenandt, 1957). Valuable contributions on the biosynthesis and distribution of these pigments in the animal kingdom were supplied by Linzen (1967, 1974). It should be added that Becker (Kühn and Becker, 1942) compared quantitatively the relation between the amounts of added kynurenine and subsequently produced pigment. The proportionality of both substances definitively abolished the gene-"hormone" concept and established kynurenine as ommochrome precursor.

2) The second line of research was likewise connected to Butenandt's laboratory. Kühn and his coworker Piepho studied the pupal molt of *Ephestia* (and *Calliphora*). They found that pupation can be inhibited when the anterior part is ligated before a critical period in the prepupa (Kühn and Piepho, 1936). They concluded, that a trigger for metamorphosis must be released from the anterior part. By carefully planned combinations of ligature, extirpation, and transplantation important steps in the hormonal control of the development of holometabolous insects could be achieved (Piepho, 1951). Becker and Plagge (1939; Becker, 1941) went on to extract and concentrate the hormone for molting and pupation. This line of research was taken over by Butenandt's institute and brought to a successful end with the isolation of ecdysone (Butenandt and Karlson, 1954) and the elucidation of its structure (Karlson *et al.,* 1965). This achievement and further investigations supported drastically the understanding of causal relationships in insect development and its genetic control (Karlson, 1963).

One may ask why Kühn did not continue the research on genetic control of pigment synthesis with the same intensity as previously. Two facts predominantly are responsible for that. First of all the situation in the "Grossdeutsches Reich" deprived him of three of his most able collaborators. Caspari was forced to emigrate in 1935. Via Turkey he arrived the USA in 1936 where he acquired high reputation as one of the most prominent geneticists. Becker (killed in 1941) and Plagge (killed in 1943) were victims of the 2nd World War. Kühn was profoundly shocked be the loss of these highly gifted and hardly replaceable

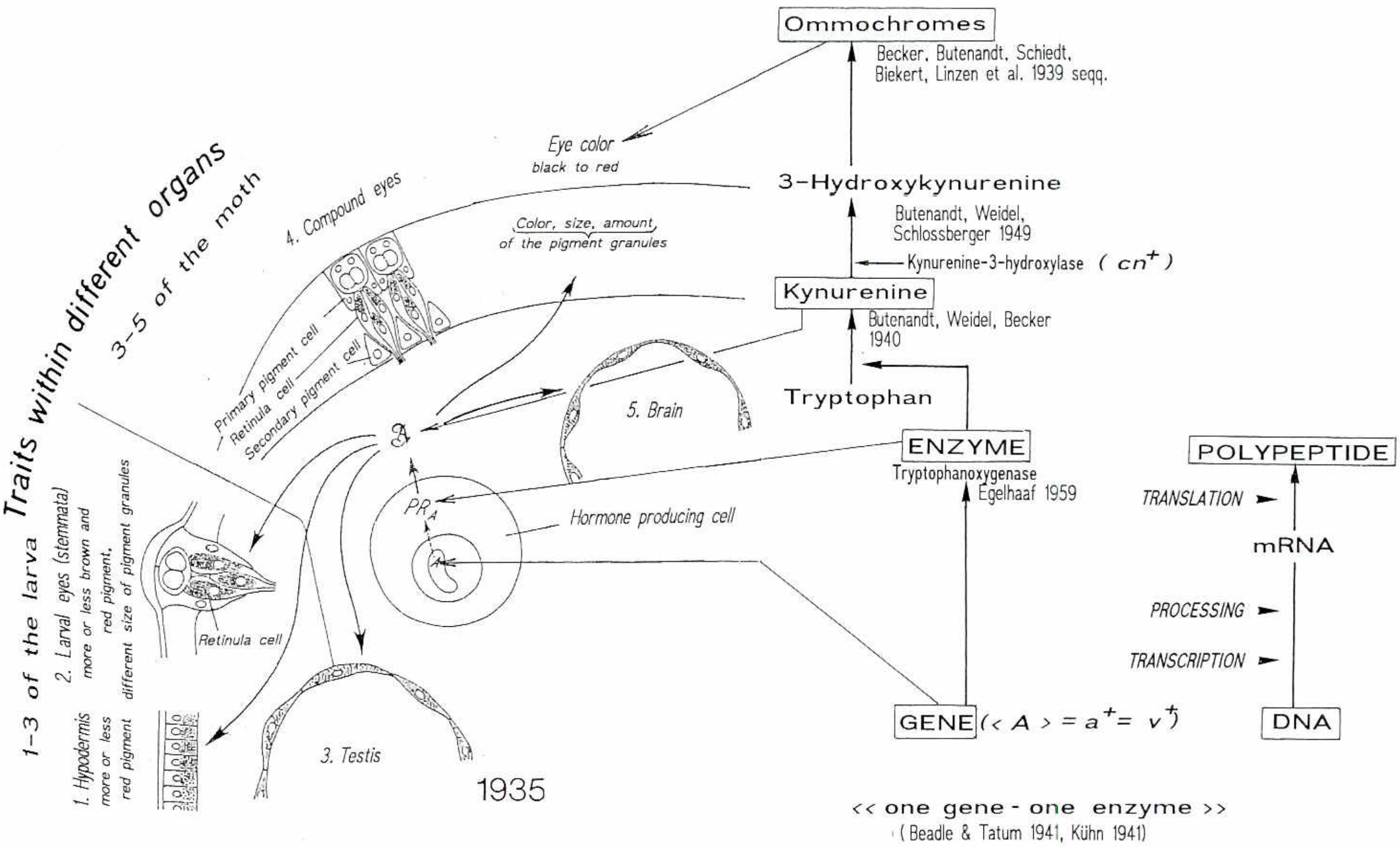

Fig. 2. On the left: diagrammatic representation of the *"A"*-gene-induced effects in different cell types of the larva and adult of *Ephestia kühniella* *(after Kühn, Caspari and Plagge 1935; legends translated to English). The original legend (omitted here) means: "Diagramm of the action of the gene A upon the phenotype by means of the hormone after transplantation of A-tissue into an a/ahost. 1-5 Sites of pigmentation.* $\mathfrak{A}_{horm}$ *= Hormone produced by the action of the gene A and released into the hemolymph. PRA= Primary reaction depending on the gene A in the cytoplasm". In the center: tryptophan-ommochrome pathway with the interacting genes and enzymes. On the right: the corresponding primary steps according to recent knowledge.*

collaborators. In addition, the prerequisites for scientific work in Germany were severely impeded during the war and thereafter.

The second reason can be seen in Kühn's different way of thinking. He considered the activity of the gene a^+ not as an isolated biochemical process but intercalated in the development of the object. His draft (Fig. 2) demonstrates this clearly. In parallel to the chemical events the structural correlates were investigated histologically and embryologically. Kühn's thoughts and his mode of exploration were concentrated on interwoven effects: "How are the temporal sequence and spatial order of precisely those conditions brought about which guarantee the proceeding normal development?" Having the cell as reacting system in mind, he wrote: "Which developmental potentials comprise the >reaction norm< of the cell of a given species and which conditions realize them?" (Kühn 1965). This more universal vision (in comparison to the ones prevailing in the USA in the thirties; Harwood, 1993) does not exclude that solving a certain problem can only be performed by the causal analysis of a clear-defined question.

Kühn's interest in biochemical genetics was revived in Tübingen by the research on pterin mutants in *Drosophila* performed by his colleague and friend Ernst Hadorn. Their collaboration, initiated in 1953, was highly stimulating and successful. Together with the chemist Viscontini they were able to demonstrate several pteridine mutants in *Ephestia* (as intermediates and eye pigments) and to isolate pterin mutants (Kühn 1956). Improved methods for analysis of the ommochrome pathway permitted the resumption of the earlier studies. For the first time in an insect an a^+-dependent tryptophan oxygenase which catalyzes kynurenine formation was demonstrated *in vitro* (Kühn and Egelhaaf, 1958). A thorough study of the pleiotropic action of the *a*-locus in *Ephestia* based on quantitative determinations of tryptophan metabolites and enzyme activities in development (Egelhaaf, 1963) enlarged the previous view considerably. Additional work on the chemical composition of pigment granules and of the systems of transport and storage of tryptophan metabolites (Cölln *et al.*, 1981; Cölln and Hedemann, 1982; Cölln, 1984) can be seen as Kühn's inheritage to scientists directly originating from his school or indirectly influenced by him (e.g. Bückmann and his students, Leibenguth, Stratakis).

It characterizes Kühn – in contrast to his older colleague Hans Spemann that he never lost the interest in his old topics in developmental biology and cytology and in his former objects (e.g. Cladocera, Hydrozoa). He resumed some of his early investigations and asked several of his students to continue. Witnessing the critical attention and strict conclusions with which he accompanied the students' progress one cannot state that he frittered away his time. Needless to say that the wing pattern remained one of Kühn's favorite objects until his advanced age. His analysis of a mosaic-promoting mutant of Ephestia (Kühn, 1960) demonstrated again the cooperation of more or less independent component areas in pattern formation by new arguments. His former assistant Viktor Schwartz (1953) drew similar conclusions when he analyzed several wing pattern mutants of the moth *Plodia interpunctella*. Thereafter the interest in this topic declined irrespective of its evident advantages. Just more recently it has been revived (Nijhout, 1985) by new concepts.

At the center of Kühn's interest, however, remained the problems of "gene physiology". He followed the rapid development of molecular biology with great attention and was deeply impressed by its progress. When comparing the new possibilities and insights with his own former attempts repeatedly the passion of the experimenter broke through, so when he aimed: "Well, now one should do... !". But never he overlooked the contemporary limitations and the still unsolved great questions. They still related to morphogenesis and to coordination of developmental events in complex, multicellular organisms. But this critical insight could never discourage him, as he wrote (1965): "The facts already known are everyone's possession; at the frontier to the unknown lies the tempting zone of the research".

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