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The history of early research

Z.UR GSTORY OF THE EARLY VIRUS RESEARCH

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Karlheinz Lüdtke

EINTRODUCTION

Scientific experiments are generally considered to have an imperative character to which the gain in logical knowledge of nature is due. Methods for adequate control and implementation of procedures and their repetition are understood as means to eliminate differences of opinion about what can be considered a "correct" expansion of scientific knowledge (see Collins 1985b: 137). When evaluating an instrument, its reliability is the key criterion with which an information transformation can be made possible, the transformation of input information about the outside world into outputs that can be recorded by our sensory apparatus1, a perspective that is used in training and cultivated everywhere, where spectacular experiments are used for demonstration purposes. In order to carry out "normal" science, this understanding, which avoids a reflection of the reality assumptions, has proven itself. From this point of view, the development of scientific knowledge presents itself as a process of a progressive elimination of subjective perceptions in favor of measurable quantities and theoretically justified invariants, as a process in which subjective constructions are constantly replaced by objective knowledge. In contradiction to this, the newer sociology of science, if it expresses itself on the connection between empirical laboratory practice and theoretical knowledge, works towards an understanding of what research objects like them that avoids a reflection of the reality assumptions, proven. From this point of view, the development of scientific knowledge presents itself as a process of a progressive elimination of subjective perceptions in favor of measurable quantities and theoretically justified invariants, as a process in which subjective constructions are constantly replaced by objective knowledge. In contradiction to this, the newer sociology of science, if it expresses itself on the connection between empirical laboratory practice and theoretical knowledge, works towards an understanding of what research objects like them that avoids a reflection of the reality assumptions, proven. From this point of view, the development of scientific knowledge presents itself as a process of a progressive elimination of subjective perceptions in favor of measurable quantities and theoretically justified invariants, as a process in which subjective

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0 This work was written during a stay of the author from July 1997 to January 1998 at the Max Planck Institute for the History of Science in Berlin. The author worked in the department of Professor Dr. Hans-Jörg Rheinberger, to whom he owes the friendly invitation and many suggestions. He also owes a great deal to Dr.Skúli Sigurdsson and Dr.Ton van Helvoort, who were always ready to discuss and critically review his manuscripts.

1 "The history of instruments shows that a general approach to improve the reability of an instrument is to narrow its application scope, that is, to make it special for a limited range of subjects ... The proliferation of instruments provides a material base for the specialization of science ”(Chen 1997: 271).

“Given” are indistinguishable from the way in which they are recognized. Scientific meanings are not something that is already contained in the facts and that is given to the researchers immovably, as if experiment and observation not only help practical abilities to reproduce examined phenomena, but at the same time reveal otherwise hidden “information” to the researchers' senses would lead to an adequate (with the phenomena "in agreement") theoretical expression (see Latour 1987: 27 and 30; Latour / Bastide 1986; Collins / Pinch 1982: 7 ff .; Collins 1985a, 1985b; Krohn / Küppers 1989: 28; Woolgar 1988: 28 f.).

The development of scientific knowledge is not due to the adaptation of interpretation patterns to existing phenomena. Rather, what is examined and interpreted is modeled by the researchers themselves. Research activity is instructed by given theories and methods of a discipline, so that the results can be traced back to a certain extent to the requirements of research. If there are any discrepancies between what was observed in the experiment and what should have occurred according to the theory, efforts are made to change the experimental procedures and conditions in such a way that the objects examined in turn change behave as expected. This connection can be fixed in the abstraction as a cycle; Collins speaks of an “experimental circle” in this regard.2 This also applies to the so-called key experiments. Gilbert and Mulkay describe how different the stories are that researchers tell about such an experiment when the audience changes, and it turns out that there are different ways in which key experiments are used to construct stories: They can be represented as whether they would have led to a theoretical version, but they can also be described as proof of the validity of a pre-defined theory (Mulkay / Gilbert 1984: 117 ff.). 3

2 He explains this using the example of the history of radio astronomy: In the late 1960s, the US physicist Weber claimed that with the help of an instrument he constructed, gravitational radiation could be measured, which at the time was not known exactly whether it actually existed. There was no unanimous opinion on the part of the physicists. Some agreed with Weber, others considered his opinion to be an unproven claim. To prove this, the developed device should have been shown to be reliable, but this had to be made dependent on whether it actually registers what should be registered - gravitational radiation. So it has to deliver "correct" results. But what is a "correct" result had to be made dependent on whether there is actually gravitational radiation,

3 Where the circle begins to tell the story is influenced by social conditions (the relationship of the narrator to the auditorium). There is a noticeable difference between whether the target group consists of closer experts with whom informal discussions can be held, or whether the audience is not so close, an audience with whom only text-based communication is used. In the latter case, the contingent origins of the experiments are hidden, in the other case “that experiments ... defined as key, not because of any particular objective features of the experiment itself or the reception the experiment received, but by the way they are presented when participants construct a particular kind of justificatory historical account ”(Gilbert / Mulkay 1984: 117 f.

Concepts that are debated in the specialist public of a scientific discipline can only be justified with reference to the applied technical procedures. Because reality is only ever experienced concretely through information processing processes, guided by the experiences and processing rules created in the subject, the proportion of what is realistic can never be exactly determined (see Graber 1984), so that in the hope of a better one Approaching the "reality" of perfection or further development of experimental techniques cannot be understood as something that would reduce the "blind spots" more and more. It cannot be determined once and for all which one is the right theory in which a phenomenon, an object is to be described. Empiricism does not control the discourse behavior of researchers in a way that excludes rivalries in how to understand the nature of an object. And so the interpretation of findings can never be brought to a final conclusion. For any given set of experimental results and empirical data, there is not just one theory that can explain it, which raises the question of whether - if observations are theory-based - theoretical differences in a given area as different interpretations of the same observation data may be understood (see Hanson 1969: 18). And so the interpretation of findings can never be brought to a final conclusion. For any given set of experimental results and empirical data, there is not just one theory that can explain it, which raises the question of whether - if observations are theory-based - theoretical differences in a given area as different interpretations of the same observation data may be understood (see Hanson 1969: 18). And so the interpretation of findings can never be brought to a final conclusion. For any given set of experimental results and empirical data, there is not just one theory that can explain it, which raises the question of whether - if observations are theory-based - theoretical differences in a given area as different interpretations of the same observation data may be understood (see Hanson 1969: 18).

A few questions now arise from what has been set out: What drives the development of theoretical knowledge if experimental and other empirical data are not sufficient to determine the theory in which they can be explained? And what exactly is the "part" to be seen in the improvement and improvement of research techniques and methods? The independence of the structure of theoretical knowledge compared to empirical knowledge does not mean that progress is irrelevant for theoretical developments that are achieved in the development of such knowledge that instructs practical-objective activities. How the transition from the level of empirical knowledge to the level of logical-theoretical knowledge takes place if empirical research practice cannot be understood as a test bench for the validity of claims that is separate from the researcher's wishes and wishes, if the idea that the repeatability of results in the experiment would create a fixed relationship between theory and observation is rejected 4 is a question that still triggers controversial debates. In the following, it will be examined using an example from the history of science. We refer to sections of the previous history of research into viral infections. that still triggers controversial debates. In the following, it will be examined using an example from the history of science. We refer to sections of the

previous history of research into viral infections. that still triggers controversial debates. In the following, it will be examined using an example from the history of science. We refer to sections of the previous history of research into viral infections.

4 According to Bijker (1994: 242), the functioning or non-functioning of a technique is not an inherent characteristic, but the result of social construction.

DIE EDETECTING A FILTERABLE INFECTIOUS AGENS AND SGet around, WHAT IS IT: A CHEMICAL SPUNCHING OR ON MICROORGANISM

The virus is determined as a biological unit consisting of nucleic acid and protein, as a complex of macromolecules, the genetic material of which consists of either DNA or RNA, and suitable host cells must be present for their replication. This (here incompletely reproduced) definition differs markedly from that which was still valid in the early 20th century: the virus was identified as a filterable, submicroscopic and infectious pathogen of infectious diseases.5 In etiological disease research There were also two other features, the ability to reproduce in the affected organism and the unlimited transferability from one receptive organism to another. This definition amounts to the verbal manifestation of a specific research practice in that it explains the pathogen through its reactions to the bacteriological experimental conditions common at the time. We are primarily interested in the transition from the early to the modern virus concept and the role that the development of procedural conditions has played.

From the beginning, very different points of view were taken on the nature of the virus. It was conceived either as a soluble substance, as an enzyme, as a ferment, as proteins of high molecular weight, which can survive a number of chemical processes without losing their infectivity (that is, organic substances that are lifeless)), or the virus was considered a particularly tiny microbe. Plant pathologists in particular concluded that there was a soluble substance or an enzyme. The history of their subject meant that they primarily thought of chemical compounds. Animal and human pathologists, who were more closely tied to bacteriology and cell culture, favored the microbe concept.

In 1879, Adolf Mayer came across the infectious character of the tobacco mosaic disease at an agricultural test station in Holland. However, he was unable to isolate a pathogen causing this disease. He initially considered that the disease might have been caused by nutritional deficiencies. However, after a comparative chemical analysis of the healthy and diseased tobacco leaves, he found that the diseased plants lacked no nitrogen, potash, lime or other substances. The soils could not have caused the disease, they were evenly fertilized and suitable for growing tobacco. Modifications in the arrangement of the manure beds (for example, variation of the heat) could also not be ascertained. Also targeted injuries to the roots of young people

5 In the second half of the last century, at the wedding of bacteriology, the term "virus" was linked to any type of infectious microscopic agent. Shortly before the turn of the century, however, following Beijerinck (1899), it was used only for filterable infectious agents.

Plants proved to be harmless (Mayer 1886: 455 f.). Mayer then made the discovery
“That the juice from sick plants obtained through friction is a safe infection for healthy plants.” If you rub a sick leaf with the addition of a few drops of water and let the resulting emulsion soak up through finely drawn-out capillary glass tubes and put them into the leaf nerves Prick older leaves, so the disease can be transferred to healthy plants (ibid., 461 f.). Mayer was now looking for “shaped content bodies”. But the infectious substance turned out to be something that couldn't be microscoped. Robert Koch's methods of cultivation on inanimate nutrient substrates - according to Koch, the cultivation of pure cultures was the actual "focus of all investigations on infectious diseases" (Koch 1912: 131) - failed.6 Mayer concluded that this could be a ferment out, because then the multiplication of the agent could not be explained. He corroborated this decision with a filtration experiment: when using double filters (consisting of filter paper) he received a clear filtrate and assumed that a non-cellular substance had passed through the paper layers. According to Mayer's report, the filtrate had no contagiousness (loc. Cit., 465). “This would preclude the possibility of an infectious effect from an enzyme-like body; because it contradicts all known properties of these strange substances to be dissolved in a liquid by simple filtration. ”His observation that the infectiousness of the juice was destroyed after several hours by heating to 80 ° Celsius he interpreted that the pathogen organizes that it must be cellular. In the end, Mayer thought of a bacterial-related illness, even though the "more detailed knowledge of the form and way of life of the culprit bacterium ... admittedly cannot be obtained in this way" and must be reserved for future research (ibid., 466).

In contradiction to Mayer, who was only aware of the contagious nature of the tobacco disease, but not the pathogen itself, the Russian plant physiologist Ivanovskij (1892) was able to prove that it is the liquid filtered from mosaic-ill tobacco leaves that gives the infection effect. Ivanovskij presented the results of his observations in an essay entitled “O dvuch boleznjach tabaka”, where, based on his own studies in Crimea and Bessarabia, and critically evaluating the observations made by Mayer in Holland, he examined the mosaic disease of the Tobacco plant described its infectious character and thereby announced the surprising fact that

6 In 1894, Behring emphasized that Koch's methods allowed “the targeted search and finding of suitable animal species for experimentally generated infections, the separation of the various microorganisms in the disease products by cultivation on solid nutrient media, and the excretion of those microorganisms which are responsible for the occurrence the specific nature of the disease is insignificant, the artificial generation of the suspected pathogens in pure culture and the exact morphological study of the same, finally the arbitrary generation of an infection by the pure cultures of the parasitic pathogen ”(1894; quoted from Zeiss / Bieling 1941: 31).

the cell sap with the pathogen passes through a bacteria-tight filter without losing virulence (Ivanovskij 1892). Such a phenomenon had not previously been encountered in the investigation of the previously known transferable agents, and it immediately posed serious explanatory problems for bacteriology. With the filtration technology used in this area, infectious material was supposed to be screened out of liquids, so that only sterile filtrates were to be expected, “waste products” that were obtained when handling infectious material and were therefore of no importance have seemed.

The Dutchman Beijerinck (1899) noticed, shortly afterwards, without knowing Ivanovskij's discovery, that a filtrate was produced in the examination of sick tobacco leaves that ran counter to this expectation. He also managed to spread the disease with filtrates from sick plants. In his experiments, Beijerinck pulled juice from mosaic-affected tobacco leaves through porcelain filters, after microscopic examination of the pressed juice and cultivations had always yielded only negative results and biological manifestations of the pathogen could not be identified. After an unsuccessful search for anaerobic bacteria7 that may have passed the filter (which were known to have extremely small, filterable spores) 8, and following the fact that no corpuscular pathogens could be detected with the microscope, Beijerinck denied the agent a cellular nature and characterized it as a living liquid infectious substance (as "contagium vivum fluidum"), as a substance that, in order to replicate, exerts its influence in solutions. He considered water solubility a characteristic of all filterable contagia. As molecular agents capable of replication, they should only be effective when incorporated into the living protoplasm of the cell.

At the time, the assumption that the pathogen was a living contagion substance in the form of a liquid met with widespread resistance because it was difficult to imagine a dissolved living substance, a substance that, although non-cellular, could reproduce. A number of researchers were more inclined to assume a contagium inanimatum. Centanni, who had identified an infectious filtrate as the cause of the chicken pest, considered the possibility that the pathogen could be a chemical agent of the type of an autocatalyst that irritated the host cells and caused a pathogenic deviation of theirs Can stimulate the metabolism to produce a substance that is identical to it. But he did not rule out

7 In the absence of oxygen (with the exclusion of air) growing microorganisms that gain their vital energy through fermentation. When breathing is carried out under anaerobic conditions, inorganic compounds instead of oxygen serve as hydrogen acceptors.

8 He also found that infectiousness could be remedied by a single application of heat at such a level that spores could not be destroyed.

At about the same time as Beijerinck, the American plant pathologist and physiologist Woods (1899) also dealt with this phenomenon, who used enzyme research to explain the phenomenon and who had come to the conclusion that the mosaic disease of tobacco was not infectious at all, but rather the result of the overproduction of certain plant-specific oxidizing enzymes, which could also be found in increased quantities in the diseased tobacco leaves. So for him it was about looking for the cause of the mosaic disease of tobacco in the plant itself and not in an exogenous agent. Woods was particularly interested in the role of enzymes in cell physiology. In the late 1990s, he dealt with the connection between certain enzymes and plant diseases, that were associated with chlorophyll destruction. The subject of his investigations was the discoloration of chlorophyll, the green dye in plant cells. Woods believed that autumn leaf discoloration could be shown to be an effect of oxidizing enzymes. In certain disorders such as tobacco disease, where the chlorophyll breakdown is clearly recognizable - the stains on the leaves can be understood as symptoms of this destruction - the enzymes oxidase9 and peroxidase10 could be the cause of the disease. Although the enzymes in question could not be filtered, they transferred to the culture medium (agar) used for the cultivation. that the discoloration of the leaves in autumn can be shown as an effect of oxidizing enzymes. In certain disorders such as tobacco disease, where the chlorophyll breakdown is clearly recognizable - the stains on the leaves can be understood as symptoms of this destruction - the enzymes oxidase9 and peroxidase10 could be the cause of the disease. Although the enzymes in question could not be filtered, they transferred to the culture medium (agar) used for the cultivation. that the discoloration of the leaves in autumn can be shown as an effect of oxidizing enzymes. In certain disorders such as tobacco disease, where the chlorophyll breakdown is clearly recognizable - the stains on the leaves can be understood as symptoms of this destruction - the enzymes oxidase9 and peroxidase10 could be the cause of the disease. Although the enzymes in question could not be filtered, they transferred to the culture medium (agar) used for the cultivation.

A microbial nature of the virus was also contested by Hunger (1905), but he rejected Woods' position on the grounds that the unlimited transmissibility of the tobacco mosaic pathogen argued against the assumption of an oxidizing enzyme. Instead, he suggested starting from a non-living "phytotoxin". This poison, which is normally a harmless metabolic product of the plant cell, causes physiological disorders (such as the mosaic disease) if it is accumulated as a result of a very high plant metabolism. The poison can then penetrate into normal cells, where it induces an additional product of poison via a physiological contact effect. The transferability should be explained by the fact that the poison has the property to act in a physiological-autocatalytic form (1905: 415 f.). That the virus of the mosaic disease was a metabolic product of the tobacco plant itself (the consequence of a pathogenic deviation in the metabolism associated with the regeneration of the irritating substance), that it thus had an endogenous origin as a product of the infected host body, became later among others also

represented by Doerr (1923). Accordingly, results from laboratory trials to produce diseases such as tobacco mosaic disease have not been the result of activation of latent infections by any which is associated with the new formation of the irritating substance), that it has an endogenous origin as a product of the infected host body, was later also represented by Doerr (1923). Accordingly, results from laboratory trials to produce diseases such as tobacco mosaic disease have not been the result of activation of latent infections by any which is associated with the new formation of the irritating substance), that it has an endogenous origin as a product of the infected host body, was later also represented by Doerr (1923). Accordingly, results from laboratory trials to produce diseases such as tobacco mosaic disease have not been obtained as a result of activation of latent infections by any

9 Enzymes that activate oxygen and transfer hydrogen or electrons directly to molecular oxygen, forming water or hydrogen peroxide.

10 Enzymes that oxidize substrates with hydrogen peroxide, whereby hydrogen peroxide is reduced to water by the hydrogen split off from the substance to be dehydrogenated.

Interventions, but interpreted in the sense of stimulating a pathological deviation in the metabolism of the respective organism (see Fust 1944: 202 f.).

Neither Ivanovskij, Beijerinck nor Woods were able to meet the demands on which the probative value was dependent on claims for the causation of infectious diseases, demands which are recorded in the so-called Koch postulates (Koch 1881) .11 Subsequently came up one also examines such difficulties in other diseases, and not only in plant, but also in animal and human pathology. Loeffler and Frosch's work on the etiology of foot-and-mouth disease, which they published in 1897 and 1898, played an important role in further virus research. They found that animals treated with bacterially sterile filtrates derived from lymph as well as the control animals treated with unfiltered lymph. Löffler and Frosch had initially expected in their experiment, the result of which they had come across, that test animals injected with bacterial-free filtrates from calf lymph were just as ill as the control animals, so that they might obtain a poison similar to diphtheria toxin. Bacteria as causative agents of foot-and-mouth disease had not been found. Various types of morphological elements can be found in bacterially sterile lymph. However, no structures to be regarded as pathogens could be detected. The surprising result that the effectiveness of the lymph was not affected by the filtration could be reproduced by experiments on numerous calves and pigs: Again and again, the bladder content of animals infected with foot and mouth disease, which had been filtered through diatomaceous earth candles, produced the same clinical picture in animals infected with it. Löffler and Frosch saw two possibilities for the explanation of this phenomenon: Either the bacteria-free filtered tissue fluid contained a dissolved, extraordinarily effective poison, or the pathogens of the foot and mouth disease, which were not found, were so small that they blocked the pores of a filter that the tiny tiny bacteria known to be able to happen. The discoverers of the filterable agent of foot and mouth disease opted for the latter option. In 1898, they wrote in a report by the German commission to research the foot and mouth

11 Koch had already noticed in a large number of later infectious diseases, which were often identified as virus-induced, that they eluded bacteriological understanding. Already in 1881 he warned against the assumption that all causes of infection were bacterial. Other microorganisms could also be effective in the animal body. At a congress in 1890, he stated that bacteriological research had failed precisely in those infectious diseases which, because of their pronounced infectiousness, seemed to offer particularly easy targets for research. "This primarily concerns ... exanthematic infectious diseases ... Even none of them have managed to find the slightest clue as to what type of pathogens they could be ...

Seek the following: “If the Commission's further investigations confirm that the effects of the filtrate, as it seems, are in fact caused by the tiniest of living things, it is reasonable to assume that the pathogens other infectious diseases of humans and animals, such as smallpox, cow pox, scarlet salmon, measles, typhus, cattle plague, etc., which have so far been searched in vain, belong to the group of these smallest organisms ”(1898: 371).

Ivanovskij had not continued the observations of the phenomenon that the sap of the mosaic diseased leaves retained their infectious properties after filtration through porcelain filters for a number of years. He only tackled it again in 1897/1898 as part of his habilitation thesis, which was published in 1902 (based on this work, he published an article in a German magazine in 1903). In this work, he also dealt with the observation results and opinions of Beijerinck (1899), Woods (1899) and Löffler and Frosch (1898), which were already available to the public at that time. He was particularly concerned with the first two researchers, both of whom, as demonstrated above, were convinced of the non-bacterial nature of the inaccessible cause of the tobacco mosaic disease. Ivanovskij did not consider Beijerinck's concept, which suggested the non-corpuscular character of the pathogen, to be mandatory. He also did not consider Woods' contested view to be valid. The artificial transferability of the disease by inoculating healthy plants over a large population and for several generations was not compatible with the assumption that it would be a plant's own enzyme, because then the infectious effect would have to be exhausted at some point . Based on his own investigations, he was convinced that it was an infectious exogenous pathogen that must be of a corpuscular nature, but cannot be grown on artificial media. Ivanovskij named the pathogen alternately virus or microbe, although he tended to believe that the agent sought could be a spore-forming bacterium.

Ivanovskij carried out various experiments to confirm his view that the pathogen was particulate. And so he looked for microorganisms that were small enough to pass through filters. As a result of microscopic studies, he noticed inclusions and crystalline deposits in the form of colorless leaflets in the cells of diseased leaves (see 1953: 109-110), in which he believed to have found the pathological origin of the tobacco mosaic disease. However, the discoverer has not yet assumed that these "Ivanovsky crystals" - as they should be called later - could be the virus they were looking for. In his opinion, a reaction of the cells to the irritation caused by the pathogens was expressed in the crystalline deposits. The in fixed and stained cells

covered and small amoeba-like structures, which he called "zooglea", which he believed to be the causative agent of tobacco mosaic disease, could not be isolated. Ivanovski proposed to understand the agent as a spore-forming microorganism. The spores, and not the microorganism itself, can be filtered. He wanted to explain the infectiousness of a filtrate that cannot be cultivated on artificial nutrient media. If the spores could only germinate in living plants or generally only under optimal conditions, this would also explain the failure of the attempts to cultivate the microbe in vitro from infectious filtrate. In heat resistance and resistance to dehumidification, Ivanovskij saw further indications that there could be spores in the filtrates.

The notion that the virus was not a living organism (a tiny bacterium, an “ultramicrobe”) but an enzyme-like substance was closely linked to the expectation that a chemically pure virus could be obtained. The understanding that the viruses were chemical molecules and that they appeared spontaneously in host bodies without exogenous infections increased in plausibility after Stanley succeeded in 1935 in presenting the tobacco mosaic virus in crystalline form. The virus identified itself as something that behaves like a chemically pure protein in all its properties, without admixtures of fat, lipids, carbohydrates and salts. One could hardly imagine such a body as an individual organism. The virus presented itself as an elongated molecule of very high molecular weight. The crystal-obtained substance turned out to be something that was between 100-1000 times more infectious than the viral plant raw material from which it was obtained. The infection power was not reduced even by repeated recrystallization. Stanley identified the virus as a globulin or protein molecule.12 After this discovery, other plant virus types also proved to be crystallizable. Finally, it was reported that chemical structure research had also shown that a number of animal viruses had a defined material composition. "... viruses such as foot-and-mouth disease and rabbit papilloma which was between 100-1000 times more infectious than the viral plant raw material from which it was obtained. The infection power was not reduced even by repeated recrystallization. Stanley identified the virus as a globulin or protein molecule.12 After this discovery, other plant virus types also proved to be crystallizable. Finally, it was reported that chemical structure research had also shown that a number of animal viruses had a defined material composition. "... viruses such as foot-and-mouth disease and rabbit papilloma which was between 100-1000 times more infectious than the viral plant raw material from which it was obtained. The infection power was not reduced even by repeated recrystallization. Stanley identified the virus as a globulin or protein molecule.12 After this discovery, other plant virus types also proved to be crystallizable. Finally, it was reported that chemical structure research had also shown that a number of animal viruses had a defined material composition. "... viruses such as foot-and-mouth disease and rabbit papilloma Stanley identified the virus as a globulin or protein molecule.12 After this discovery, other plant virus types also proved to be crystallizable. Finally, it was reported that chemical structure research had also shown that a

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12 Bawden, Pirie et al. later objected (1936) that they had discovered phosphorus in the crystalline substance obtained from mosaic tobacco plants and that this element was contained in the form of nucleic acid. They wondered if the crystalline substance they had isolated was the virus itself or not. For them it had not yet been proven that "that the particles we have observed exist as such in infected sap" (ibid., 1052). Stanley has agreed that the isolated substance does not consist solely of protein. After that, his research results were widely recognized. A few years later, Schramm reported that the tobacco mosaic virus is still capable of producing a new generation of viruses even if its protein coat has been chemically modified and pieces have been broken out of it. Schramm disassembled the particles with weak alkali. Nitrous acid was then added, after which the particles could be restored to their original shape. But they no longer contained nucleic acid, and they were no longer capable of replication, from which it could be concluded that the protein in the virus does not contain the information for its reproduction. In 1955/56, Schramm, together with Gierer, succeeded in obtaining the protein-free RNA of this virus by adding phenol to a tobacco mosaic virus suspension. With this "pure" RNA it could be shown that it alone contains all the information for virus replication (note from Munk 1995: 37 f .; without source). Independently of these examinations, Fraenkel-Conrat also came to the same conclusion at the Virus Laboratory in Berkeley near Stanley.

are in no way inferior to the tobacco mosaic virus. When examining the insect's disease, it was found that the polyhedra occurring in the caterpillars, which are infected with viruses, are probably to be understood as crystals of pure virus proteins. So these animal viruses are chemical compounds and not organisms, ”says Schramm (1942a: 258). And in another article of the same year it is stated that a protein which was completely uniform in terms of molecular weight had been isolated from the blisters of the cattle suffering from foot-and-mouth disease. A uniform protein was also obtained from the warts of the Cottontail rabbit. They should be viewed as chemical molecules, even if it has not yet been possible to obtain them in crystallized form (Schramm 1942b: 793) .13

The disease-causing effects of filtrates could subsequently be demonstrated in a number of other types of infection without successively approaching a uniform view of the nature of these pathogens with the accumulation of empirical knowledge. It remained open whether such tiny infectious agents are really microorganisms or mere chemical substances. Whether this or that position was taken or rejected - empirical evidence could be presented in both cases for defense and for attack purposes.

On the one hand, the microbe nature of the virus was supported by the unlimited transferability of the infectious diseases caused by filterable pathogens from one susceptible individual to the other, each time requiring only minimal amounts of substance, which had to be diluted considerably in the body of the recipient. It was conceivable that even the most effective substance would become ineffective as a result of this continued dilution, unless an opposite process intervened, the ability to increase in quantity by itself, assimilation of foreign substances while constantly preserving the original Properties to increase, but this was only considered an attribute of the living substance (see Doerr 1923: 909).

Because the various types of virus could be inactivated ("killed") by certain physical and chemical influences (so that the modified material was no longer infectious) without affecting the chemical and serological properties and the shape of the microscopic crystals - they were preserved - also supported the understanding of the virus as a microbe: that bacteria are robbed of their ability to reproduce and thus also of their infectiousness by killing them, without the chemical composition of their body

13 An animal virus only crystallized in 1955, namely that of the polio virus (Schaffer / Schwerdt 1955).

Microbiologists and immunologists were familiar with modifying the punch in a recognizable way and without affecting the antigen functions in any way.

Burnet and Andrewes referred to “the occurrence of immunologically or functionally different types, the transmission of which always maintains the original type within fairly wide limits. Every type of foot-and-mouth disease virus causes the same clinical picture in guinea pigs, and yet the immunological character of the different types remains unchanged, regardless of whether the passage takes place in guinea pigs or in another susceptible animal ”(1933: 169; see also Munk 1995 : 7 ff.). With herpes, according to Burnet and Andrewes, it is possible "to obtain, through suitable passages, those strains that ... are neurotropic or dermotropic and ... reproduce with these properties." The same characteristic was demonstrated by poultry tumor viruses and bacterial viruses (these types are discussed below), “A property that is probably common to all living organisms of any kind. Each pure passage strain will have certain inheritable, characteristic ... characteristics that are independent of the surrounding milieu and distinguish it from other strains. "The occurrence of such type individuality in the case of transmissible pathogens of the type in question suggests that" it is are independent microorganisms with self-propagation ”(ibid.).

Gratia (1921: 217 ff.) Considered the idea of the virus as a metabolic product to be justifiable only if it could be demonstrated that the process is always of the same type as host cells; how else could one and the same protein, if it acted as a stimulus, modify the metabolism in the same way and with the formation of identical metabolic products. Viruses would, however, retain their original character in serial transmission even if the host species changes - an unmistakable hallmark of autonomous behavior. For him, the fact that, for example, herpes virus only ever becomes herpes virus, regardless of whether it reproduces in human skin or in the rabbit brain, was proof against the concept of endogenous virus formation. A relationship in chemical or serological terms of the virus protein with the normal protein of the host, which would have supported the hypothesis of endogenous virus production, did not succeed. For example, Chester (1936) was initially convinced that, with the help of complement fixation and anaphylaxis, he would have demonstrated crossed reactions between the crystalline mosaic virus protein and normal protein in the tobacco plant. However, it emerged from tests that the preparations of the virus protein were contaminated with normal protein (see Doerr 1938: 36). Seiffert referred to immunity research: “Based on immunity research, we know that every virus that has been investigated in this direction to date has its own antigen structure. Vaccine virus, obtained from humans, cattle, rabbits, from tissue cultures,

Reactions with immune sera. From a biological point of view, it would be even more difficult to see that a virus of completely the same protein structure should be formed in cells from so different animals in a very uniform manner. The same applies to the very small foot-and-mouth disease virus. It is quite unlikely that its three types, which can be separated serologically in terms of their structure, in cattle, in guinea pigs and in culture, can be produced quite uniformly. This kind of virus formation from the components of the cells is much more difficult to grasp than the equally incomprehensible self-propagation of Vira, which apparently are pure protein molecules ”(1938: 9).

Cases have also been known that one and the same plant is infected simultaneously with two or more types of virus, for example the tobacco with mosaic virus and ring spot virus. In such cases, one would have to assume, following the idea of endogenous virus formation, that pathogenic protein metabolism in the same host can produce several types of high molecular weight proteins, which nevertheless retain their special properties, since they can be isolated by a number of methods . This made it difficult to adapt the observed facts to the idea that virus types are nothing more than protein molecules (see Smith 1935: 21 ff.).

The view that the filterable pathogen was a microbe could be made credible by referring to its ability to change and adapt. With regard to the tobacco disease, it could be said that “in addition to the usual light and dark green spots, there are also seldom yellow ones. If these are now cut out and inoculated onto other plants, the yellow variant appears alone. Now it could be that the first plant had three different types of the virus from the start. However, if you switch the green virus, which always stays green with the same type of tobacco, to a different type of tobacco, yellow spots suddenly appear. So environmental change matters ”(Heilmann 1940: 657).

But there were also empirically supported arguments to defend the concept of endogenous virus production and to support the idea that the virus was a contagium inanimatum, a single protein that was effective as an organic autocatalyst. The understanding of the virus as a filterable microbe has been questioned by some virus researchers simply because, in their opinion, submicroscopic dimensions were incompatible with the minimum of organization and structure that, according to widespread belief, was to be assumed in the case of a lively “wholeness”. Guided by the prevailing teaching that living things have to be cellularly organized, it seemed more plausible to interpret the phenomenon as a chemical substance because tiny cells,

difficult to imagine. The filterable agent also seemed far too small to do that
Satisfying the "space requirement of protein" (Errera 1903: 73) without which life was unthinkable. Even in the 1930s, it was still a mystery to many people how a particle consisting of a few molecules could be designed in such a way that it was able to perform all the complex functions of a living, autonomous organism. Elemental organisms seemed to be at least large enough to meet this requirement.14 Andriewsky (1915: 90) found that the chicken pest virus passed filters that retained hemoglobin. The diameter of the hemoglobin molecules was given as 2.3-2.5 mμ, and Andriewsky therefore concluded that the molecules or micelles of the virus would have to be even smaller so that the virus particles could not be constructions,

The existence of living things with submicroscopic dimensions could also be questioned with the argument that the pathogenic ultramicrobes, if they existed, should be opposed to saprophytic organisms that are easily grown in vitro. One could point out that all efforts made at that time to prove them had been unsuccessful (Molisch 1919) .16

14 Later investigations by Stanley (1935), Best (1936), Beard and Wyckoff (1937) showed, however, that even small virus types such as the virus of the mosaic disease of tobacco or Shope's rabbit papilloma contain protein. According to another variant, the impossibility of imagining a cell with such tiny dimensions that even the indispensable protein, the absolutely necessary building material of every cell, could no longer be a problem if the elementary particles were not just cells , but could be understood as molecules.
At the time, the idea that the cell represented the most primitive, indivisible basic form of all life had largely been abandoned. First of all, structures of the cell plasma, such as the granules (mitochondria), were determined as independent organisms (symbionts) that were originally alien to the cell but had become dependent on it (Buchner 1930: 809 ff.). Or the cell structures were probably seen as the cell's own form elements, but they had a certain independence of life functions within the cell structure. Morphological cell research, and above all the investigation of the processes involved in mitotic cell division and fertilization of the egg cells, had to give new impetus to the idea that the cell was not a unit, but already a complex of much smaller units.

15 In view of this, he felt tempted to agree with the contagium vivum fluidum hypothesis. However, the hypothesis of the “living protein molecule” was linked to the difficulty of how isolated protein molecules can be ascribed the ability to eat, multiply, inherit and adapt. It has also sometimes been considered that the virus may correspond to a boundary state between the animate and the inanimate, that they are tantamount to molecules or groups of molecules.

16 No compelling conclusion for Doerr, because it cannot be ruled out that there are only pathogenic ultra microbes. "... these forms of life then sink back to mere regression in the phylogenetic view and would not have removed the importance for the question of the origin of life and the problem of abiogenesis like the opening up of a world of ultra samples" (1923: 910).
To defend the view that the viruses are microbes, the idea was also developed that viruses may not be capable of saprophytic growth because they would have suffered an unusually high loss of the necessary enzymes during development, so that they had become obligatory parasites - a variant of the explanation still fought in the 1950s, according to Pirie (1973: 45, reference from: van Helvoort 1994a: 199; see also Hershey 1957: 230 f.), which made it possible on Understanding of the virus as the simplest form of life, despite the lack of evidence of saprophytic growth, which included the notion that it had already been criticized in the late 1940s that virus multiplication was due to cell division.

The fact that the infectiousness could only be transmitted artificially was used as an argument against the assumption of a microbe nature of the virus. Given the artificial transmission, hunger seemed more apt to start with a poison capable of causing physiological contact in normal cells, with the result that the same toxin is formed there secondarily. The toxin of the mosaic disease has the property of acting in a physiological-autocatalytic way (1905: 296). Baur also believed that the artifical transferability of the disease was something that would not be compatible with the microbe nature of the virus (1904).

Virus types such as cowpox showed behavior against mechanical, osmotic and chemical effects, which made the existence of a surface membrane questionable, but which most microorganisms have (see Schramm 1942b: 794).

The type of their composition was regarded as an experimentally testable criterion for the assignment of the viruses to the organisms or to the chemical agents, whereby uniformity and a defined chemical composition suggested the latter variant, whereas a dimensional variability of the virus elements, which some researchers wanted to have observed was rather interested in recognizing the character of organisms in these structures. A proliferation by cell division should lead to heterogeneous virus particles, whereas a broad homogeneity, as Svedberg and Erikson-Quensel wanted to determine in the tobacco mosaic virus in the ultracentrifuge and electrophoresis (1936; note from: van Helvoort 1996: 288) 17, as a property a chemical substance. Thereby,

17 Against the idea that the virus had proven to be lifeless with its crystallizability, several analogies could be put forward which suggested that a crystalline structure can be compatible with vital properties and functions. "One of the best known examples of
"Biocrystals", says Doerr (1944a: 44), "are the muscle fibers ...; The carriers of contractility are the elongated thread molecules of myosin, a globulin-like, strongly birefringent protein body, which, in a suitable experimental arrangement, provides the same X-ray diagrams as the muscles themselves ...
% solution shows the myosin ... the ability to solidify into a gel on standing; shaking destroys this regular arrangement by throwing the thread molecules together, thus liquefying the jelly. In an analogous manner, the elongated and thin particles of phytopathogenic virus proteins are stored in parallel to each other, only that higher concentrations are required than with myosin ... There are multiple and noteworthy relationships between the myosin and the crystalline virus proteins, this applies to an increased extent to another biological counterpart, namely to the heads of the spermatozoa, the substance of which has the properties that demonstrate the paracrystalline structure, and of nucleoproteins, probably in the form of thread molecules. ”

should be understood. ”The ability to crystallize“ generally only belongs to chemical molecules, but not to the complex organisms ”(also, 792). The chemical composition of the agent should "be variable within certain limits and (should) not (be) defined so that the assignment of a chemical formula seems reasonable" when it comes to individuals of a "weighable amount of microorganisms." same kind ”acted. However, the construction of a crystal lattice presupposes extensive agreement and great regularity in the structure of the individual particles (also, 791).

DIE EDISCOVERY OF "BACTERIOPHAGY"

A special chapter in the history of virus research was ushered in at the end of the 19th century with the discovery of bacteria-dissolving substances. The resolving element, the "Bacteriophage", which was also called "lytic agent" or "bacteriophages lysate" (from Preisz 1925: 2), had dimensions that were also attributed to the particle size of a large number of animal and phytopathogenic virus types (see among others Elford / Andrewes 1932; Schlesinger 1932). He passed through porcelain filters and needed the presence of bacteria to grow, just as a virus could only be grown in the presence of living cells. And with the same techniques that allowed the chemical purification of different types of virus, it was also possible to obtain purified concentrates from phage suspensions, the effectiveness of which was up to six powers of ten higher than that of the starting solution (see Schlesinger 1934; Northrop 1938) and how animal and plant viruses appeared they are also chemically similar, that is, to consist of nucleoprotein (see Alloway 1933: 255). Some researchers have therefore classified the phage as a virus-like phenomenon (see Seiffert 1938: 194; Bloch 1940) and named it “bacterial virus”. The above-mentioned analogies suggested that studies should be carried out to find out to what extent bacteriophagy processes can be equated with infection in viral diseases and whether the phages also behave virus-like in other, more biological ways.
ten (see Bloch 1940: 481) .18

Bacteria-changing (- "damaging" and -dissolving) substances were first observed in the late 1980s. Nuttal (1888) and Buchner (1889) reported a bacteria-destroying effect of the blood serum on the typhoid bacillus, this effect being attributed to the protein contained therein. Kruse and Pansini reported the disappearance of pneumococci in older broth cultures that had stopped growing (1892). In 1899, findings were reported that bacteria would dissolve due to pyo-cyanase (Emmerich, Loew 1899) .19 Conradi and Kurpjuweit

were able to demonstrate in the cultures of bacteria from the typhoid coli group the presence of selectively growth-inhibiting, thermolabile substances which were also found in the intestinal content of humans, substances which, in their opinion, were formed by the bacteria in the course of their growth and in the near future Relationship to intracellular enzymes. To name such "inhibitors" they proposed the term "autotoxins" (1905a: 1764; see also Conradi / Kurpjuweit 1905b).

In 1915, Twort, a British bacteriologist, reported that he had seen the appearance of a transmissible bacterial dissolution, the continued transferability of antibacterial effects from one quantity of culture medium to another. The thermolabile agent capable of bacterial dissolution (lysis) was still effective in high dilutions (transfer of small amounts of a lysed to a fresh broth culture) and could be filtered through pores of porcelain lantern candles (Berkefeld candles). Twort initially aimed at the following: It was a matter of proving the existence of filterable ultramicroscopic microorganisms20, i.e. of viruses, not only in pathogenic material (for example in calf lymph), but also in soil, manure, etc. The existence of saprophytic ultramicrobes became at that time for kept very likely.

18 There was also a practical interest in the question of whether phage can be used as a model object for virus research, on which essential aspects of virus behavior can be studied. A large animal colony was required to test a virus suspension that had to be tested against animals. In addition to the associated expenses and the problems that resulted for the controllability of conditions of the experimental procedure, there was also a relatively long period of time which was used for a single examination, whereas checking a phage suspension only took a few hours had to. “Working with plant viruses such as the tobacco mosaic virus was in the middle of the time between animal viruses and phages in terms of the time and the amount of laboratory work required. It was clear from this point of view that the bacteriophage was by far the best material. So it made sense to try and learn everything possible from this easy-to-use experimental subject before moving on to more difficult viruses that plant or animal substrates require for testing, ”said Ellis, who had specifically looked at virus-induced cancer growth (<1966> 1972: 63).

19 Antibiotic metabolic product of Pseudomonas seruginosa, a species in the genus Pseudomonas, is an inflammatory, mixing agent. Emmerich and Loew mentioned the following experiment with swine bacilli bacilli: Agglutination and sedimentation occurred in broth culture of these bacteria over time
a. Was 1 cm3 of the liquid above the sediment clouded by agglutinated bacterial flakes
brought into new broth, agglutination and sedimentation also occurred during the incubation in a period that was becoming shorter and shorter. Repeated transmissions resulted in the dissolution of the entire sedimented bacillus mass. Ultimately (as Emmerich and Loew thought by accumulating bacteriolytic enzymes), it was no longer possible to transmit the culture at all.

20 According to Burnet and Andrewes (1933: 162), all viruses that are “smaller than 0.2 µ” could be described as “ultramicroscopic”. However, this did not mean that they had to be outside the light microscope's visualization. “Characteristic tiny bodies have been observed in several viral diseases and appear to be causally related to the infectious properties of the material. They can be brought into the visibility range of the microscope in various ways ”(ibid.), For example by using suitable staining methods in smears.

to justify empirically. Twort's initial assumption was that if non-pathogenic variations occur in nature, they should probably be easier to cultivate than pathogenic ones. Attempts have been made to grow them from such materials as manure, grass, water, etc. on tested and specially prepared media (agar, serum, etc.). Different amounts of chemicals or extracts (mushrooms, seeds) were added to them. The material to be tested for viruses was mixed with water, heated to 30 ° C (also at different times) and then filtered through a candle. Then different media were inoculated with the filtrate.

However, these experiments showed no growth of the filterable virus. Various animal experiments were also carried out in the hope of triggering the virulence filter-passing virus. But the results have always been negative. It was never possible to grow a filterable microbe ("a true filter-passing virus") from the filtrates by re-vaccinating them on the various culture substrates. However, there were results that were not originally intended, results that occurred during the investigation into the possibility of growing filterable germs, for which Twort had sown glycerated calf lymph on agar. Inoculated agar tubes, after being warmed to 37 ° C for a day, showed growth of coconut colonies that initially looked white and opaque (watery looking areas), but most of which appeared glassy after some time. If smears were made from the colonies, which were only slightly glassy, opaque and glassy colonies resulted. If, on the other hand, a trace of a glassy one was brought to the edge of an opaque colony, the glassy dissolution of the colony began from this point. The whole colony appeared glassy after a short time and consisted microscopically of the finest granules that could be stained according to Giemsa (and no longer of cocci). Twort demonstrated that the active agent of such transparent colonies can be filtered. Experiments with certain bacilli of the typhoid coli group led to comparable results. If, on the other hand, a trace of a glassy one was brought to the edge of an opaque colony, the glassy dissolution of the colony began from this point. The whole colony appeared glassy after a short time and consisted microscopically of the finest granules that could be stained according to Giemsa (and no longer of cocci). Twort demonstrated that the active agent of such transparent colonies can be filtered. Experiments with certain bacilli of the typhoid coli group led to comparable results. If, on the other hand, a trace of a glassy one was brought to the edge of an opaque colony, the glassy dissolution of the colony began from this point. The whole colony appeared glassy after a short time and consisted microscopically of the finest granules that could be stained according to Giemsa (and no longer of cocci). Twort demonstrated that the active agent of such transparent colonies can be filtered. Experiments with certain bacilli of the typhoid coli group led to comparable results. that the effective agent of such transparent colonies can be filtered. Experiments with certain bacilli of the typhoid coli group led to comparable results. that the effective agent of such transparent colonies can be filtered. Experiments with certain bacilli of the typhoid coli group led to comparable results.

Twort also found that these processes are faster and more comprehensive when fresh and young cultures are used instead of old ones, and that little was stirred in cultures that were dead or young that had just been killed. The glassy material easily passed through the finest filters when diluted with water. And a drop of filtrate, transferred to an agar tube, was sufficient to make the tube unsuitable for micrococci. At first there was growth, but soon glassy spots appeared which then expanded. The number of points depended on the dilution of the glassy material. In some cases it was so active that growth stopped and that phenomenon took effect immediately. It turned out

When trying to draw definitive conclusions from the results, Twort had initially considered that he had grasped the effects of an ultramicrobe. In the end, however, he saw an autolytic principle (ibid., 1242 f.).

The phenomenon of transferable bacterial dissolution was also described a few years later by the Canadian bacteriologist d'Herelle. He had observed that the filtrate from the Ruhr convalescent chair was able to dissolve living Ruhr bacilli in culture (1917; published in 1922). D'Herelle carried out the following experiments: Drops from the bowel emptying of a Ruhr patient were added to a sterile broth. The mixture was then placed in an incubator for an entire day. Then he filtered it through a Chamberland candle that holds back all bacteria. In the next step, a portion of the clear filtrate liquid (10 drops) was added to a fresh, sterile broth tube inoculated with bacterial dysentery (Shiga bacilli) and also incubated. Normal darkening in the tube initially occurred after the added Ruhr germs had increased (after incubation). It was then filtered again and part of the filtrate was added to a new tube and so on. Surprisingly, one day the tube from the last attempt remained clear (sterile). In a control tube (without the addition of filtrate), which had also been loaded with bacilli, the germs reproduced normally and the broth became cloudy. This proved to d'Herelle that something can be filtered out in the stool that dissolves the bacilli and that, as could be deduced from the dilution series, multiplies. Surprisingly, one day the tube from the last attempt remained clear (sterile). In a control tube (without the addition of filtrate), which had also been loaded with bacilli, the germs reproduced normally and the broth became cloudy. This proved to d'Herelle that something can be filtered out in the stool that dissolves the bacilli and that, as could be deduced from the dilution series, multiplies. Surprisingly, one day the tube from the last attempt remained clear (sterile). In a control tube (without the addition of filtrate), which had also been loaded with bacilli, the germs reproduced normally and the broth became cloudy. This proved to d'Herelle that something can be filtered out in the stool that dissolves the bacilli and that, as could be deduced from the dilution series, multiplies.

D'Herelle determined that this substance could be grown in series. If a suspension of fresh Shiga bacilli (obtained from an ordinary agar culture) was sown into the tube in which growth had failed to occur, these germs were dissolved after several hours; the tube appeared perfectly clear. In detail: D'Herelle mixed a fresh broth culture of bacilli with a drop of the dissolved culture. After 15 hours this was also solved. In the same way, he added a drop of the dissolved culture to a new flood and so on. Instead of weakening, the lytic effectiveness accelerated after each passage. This means that the more passages had taken place until the minimum level was reached, the less time it took to dissolve, that no longer changed. This serial continuation of the lytic principle and its multiplication when the bacteria dissolve was now evaluated by d'Herelle - contrary to Twort's view - as proof that it was a being living at the expense of the bacteria, a parasite of the bacterium (d'Herelle 1922), so that their study was the study of "the pathology of bacteria" (d'Herelle 1921:

665). The size of this “ultramicrobe”, which he also called “a living colodial micell” in one of his essays (1928: 541), would not exceed that of a protein molecule (1921: 664).

Another attempt should support this thesis, an attempt to make the bacterial-dissolving effect visible on solid nutrient media: D'Herelle added a small amount of a dissolved culture to a broth culture of Ruhr bacilli (about 0.00001 cm3). Thereupon, immediately after and after one, two and three hours of incubation, a drop of it was spread out on a bacillus lawn (on inclined agar tubes). The variation of the contact time led to the following results: In the first tube (without incubation), the agar was covered with a normal bacillus lawn, which had two holes, that is, places where no bacterial growth was noticeable. The inoculated tube after one hour of incubation showed six holes, the inoculated after two hours showed only one trace, that inoculated after three hours had no culture at all. If a tube containing Shiga bacilli and a few drops of a dissolved culture was left to its own devices, after clarification, which indicated sterility, a secondary clouding occurred some time later, caused by Shiga bacilli, which was compared to the dissolving one Effects were obviously or had become resistant. D'Herelle interpreted the results of his experiments as confirmation of his view that what dissolves the bacteria increases and takes on visible forms. From the "holes" he concluded that colonies formed with the multiplication and therefore it could only be a corpuscular being. The lytic agent, which he assumed was not only found in chairs of convalescent convicts, but was widely distributed in nature,

The opponents of the d'Herellian position - after Hoder (1932: 4), Otto and Munter (1928: 410) and von Gutfeld (1925: 413) they formed the majority of the researchers21 - saw a bacterial decay product in the phage. And so a large number of researchers reported that they had made "lysine" from bacteria alone: Gildemeister and Herzberg reported in the mid-1920s that they had examined "spontaneous lysine formation" under the influence of varied culture conditions (es culture media, temperature and time were varied), and the investigations had shown that the bacteriophages originated in a bacteriophage-sterile reaction space, the spontaneous lysine formation being governed primarily by temperature (1925). It was claimed by Rosenthal (1926: 612) that he came from phage-free cultures (Ruhr, Typhus,

21 According to Doerr, however, the majority of phage researchers were undecided (1923: 909).

so that a spontaneous phage formation must be assumed. Bordet and Ciuca, who blamed the d'Herellean phenomenon of a bacterial metabolic disorder (“vicification nutritive”), stated that after repeated injections of normal coli bacteria into the abdominal cavity of guinea pigs pretreated with coli culture, a transferable lysine for form the coli strain used, which can easily be obtained with the exudate. This means that they claimed to have obtained a lysine directed against coli bacilli experimentally from that peritoneal exudate without using stool filtrates (1921). These or those conditions were then identified by the experimenters, whereby normal bacteria under special,

Researchers who were convinced of endogenous virus formation relied primarily on concepts of a biochemical type (fermentation theory, catalyst theory, theory of protein and the like) and understood the lytic element as an enzyme that produces the bacterium, which is therefore its own Destruction causes, according to Hoder (1932: 13), to make use of an analogy to secretion processes in yeast types and to the autolytic enzyme action in yeast cultures (see Preisz 1925: 90) or the lytic ability of some fungi (self-poisoning , digestion). Some researchers have introduced phage as a metabolic bacterial toxin that is regenerated by the diseased bacteria (including Doerr 1922). For Kabéshima (1920), this was just a normal, inanimate bacterial ferment, that is released through autolysis. He suspected that the bacterial dissolution was caused by leukocytes. Kuttner (1921a: 1921b) reported that he had obtained a bacterial-dissolving filtrate from leukocytes, from intestinal mucosal cells and from guinea pig liver cells, which had a dissolving effect on typhoid and dysentery germs (shiga bacilli). According to Proca (1926: 125, 153), lysine was an endotoxin or intracellular ferment. Von Gruber and von Angerer saw in the "lysine" digestive enzymes that were already present in normal bacteria and that would normally only not be effective (von Gruber 1923: 204 f .; von Angerer 1923: 205 f.). Von Gruber recalled the self-digestion of the yeast press juice by the endotryptase and the rapid flow of the yeast under the influence of small amounts of benzene, ether and others Here reference was made to Ehrenberg's observations with regard to protein enzymes (1922: 432). In his experiments, Ehrenberg was able to artificially “cultivate” and continue the protein ferments with a certain degree of specificity, whereby filtration had proven to be beneficial for the fermentation. Because of this, Otto and Munter determined the “biological

Nature of bacteriophage lysine ... due to its chemical-physical behavior as a high molecular solution of bacterial protein ..., the properties ... of which can be explained by laws, how they master the colloidal solutions ... "(1928: 400). The bacterial dissolution should be initiated and maintained by the decay of the living bacteria into inanimate, fermentative protein particles (Otto / Munter 1923: 403); Otto and Munter identified the bacteria-dissolving substances as the “smallest bacterial protein particle (s) with fermentative properties” (1928: 410 ff.). Bail (1925), who favored the idea that the bacteriophage was part of the generative substance of the body of the bacteria, thought of the splinters of cells (especially chromosomes) that have become free: Due to the protective forces of the body, the bacilli are broken down, whereby these lose certain properties, sometimes even down to the "splinter size", so that they could pass through bacteria-proof filters. If such fragments, which were probably still viable, were brought together with normal bacilli, they would withdraw the substances lost during the breakdown and make these bacilli again.

Another representative of an understanding of phage reproduction based on the theory of enzymes is Northrop, who dealt with kinetic enzyme studies in the 1920s, during a period in which the protein nature of the enzymes had only been proven.22 For isolation and purification of enzymes, Northrop worked with methods and procedures that had previously proven themselves in the chemical isolation of enzymes (such as crystallization and salt fractionation). The investigations produced crystalline products which, however, showed no enzymatic activity. It was revealed that these products were precursors of proteins with such activity, and their autocatalytic properties could be demonstrated. 23 For Northrop, autocatalytic processes provided a suitable starting point for interpreting biological phenomena such as protein synthesis and propagation in the context of biochemistry and physiology. And similar to how active enzymes are formed via autocatalysis, Northrop also imagined the formation of phages (Northrop 1937; see Olby 1974: 149 f.), Which for him and his team could not be a living and complex organism (Krueger / Northrop 1931 ; Krueger / Scribner 1939; note from: van Helvoort 1994b: 108). According to this concept, the phage develops from a precursor that is already present in the bacterium And similar to how active enzymes are formed via autocatalysis, Northrop also imagined the formation of phages (Northrop 1937; see Olby 1974: 149 f.), Which for him and his team could not be a living and complex organism (Krueger / Northrop 1931 ; Krueger / Scribner 1939; note from: van Helvoort 1994b: 108). According to this concept, the phage develops from a precursor that is already present in the bacterium And similar to how active enzymes are formed via autocatalysis, Northrop also imagined the formation of phages (Northrop 1937; see Olby 1974: 149 f.), Which for him and his team could not be a living and complex organism (Krueger / Northrop 1931 ; Krueger / Scribner 1939; note from: van Helvoort 1994b: 108). According to this concept, the phage develops from a precursor that is already present in the bacterium

22 Sumner (1926) succeeded for the first time in isolating the urea-splitting enzyme urease, displaying it in crystalline form and identifying it as a protein. It was not until the early 1930s that Northrop also provided evidence of crystalline pepsin and trypsin. Crystallization of the proteolytic enzymes pepsin, trypsin and other proteases has been widely valued as a major advance in the study of biochemical processes. Because in the 1930s it was still not possible to have clear ideas about protein formation in general and about the formation of enzymes in particular. One explanation was that the proteolytic enzymes involved in protein degradation also played a role in their synthesis.

23 That is, for some enzymes, the transformation of the precursor in the enzyme occurred under the influence of the active enzyme, which allowed the conclusion that the formation of these enzymes is an autocatalytic process.

is, in a reaction analogous to the conversion of pepsinogen and trysinogen into the relevant enzymes in vitro (see Krueger 1937: 379) .24 That resting bacterial cells to a certain extent produce precursors of phages, which convert to such in the presence of active phages , Doerr (1938: 65) probably considered a "rather dubious hypothesis". But even if you don't join her, you have to acknowledge the importance of the experimental results, “if they should stand up to careful review; in any case, they speak against the fact that the phages can be exogenous parasites of the bacteria. ”Corresponding investigations were carried out in order to isolate the phages in pure form and to prove the existence of phage precursors. Results of investigations of what a staphylococcal strain had been used for were used to justify the judgment that, in the case of staphylococci, when they multiplied, a pre-phage stage developed which, when brought into contact with phages, even converted into phages.25 The phage formation was caused by a rapid increase in phage titer in the Phage mixture identified. That Northrop turned to the phage resulted from the fact that the bacterial virus presented itself as a prototype for the study of protein synthesis, especially since he was able to rely on researchers such as Twort, Gratia, Bordet and others who produced phages for bacteria Had kept enzymes. 26 25 Phage formation was identified from a rapid increase in phage titer in the precursor phage mixture. That Northrop turned to the phage resulted from the fact that the bacterial virus presented itself as a prototype for the study of protein synthesis, especially since he was able to rely on researchers such as Twort, Gratia, Bordet and others who produced phages for bacteria Had kept enzymes. 26 25 Phage formation was identified from a rapid increase in phage titer in the precursor phage mixture. That Northrop turned to the phage resulted from the fact that the bacterial virus presented itself as a prototype for the study of protein synthesis, especially since he was able to rely on researchers such as Twort, Gratia, Bordet and others who produced phages for bacteria Had kept enzymes. 26

A number of researchers soon incorporated observations of bacterial variability into the study of the bacterial-resolving phenomenon27, following the notion that bacterial properties were caused by phage activity, properties that were preserved over several generations, so that it also seemed to be permissible to "speak of an inheritance of the properties and to assume that the phage in question genetically modified the bacterium" (Hoder 1932:

24 According to Krueger (ibid.), The conversion into phages could either be based on hydrolytic protein cleavage or be the last phase of a synthesis in which the full phages would act as a catalyst. These statements were mainly based on studies that succeeded in isolating staphylococcal phages in the form of a nucleoprotein, so that their precursors could also be ascribed protein character.

25 However, the theory of the existence of a phage precursor was only based on work with one and the same staphylococcal strain and an associated phage. There have been no attempts to detect precursor stages in other phage species.

26 "The multiplication of bacteriophage during bacteriophagy, combined with the supposed non-living nature of bacteriophage, constituted an interesting issue for Northrop" (van Helvoort 1994b: 106).

27 As Fleck explains, the first detailed observation of the variability related to the so-called bact.coli mutabile. The observers (Neisser and Mansini 1906) would have examined cultures contrary to Dogma here both after 24 hours and after a few years. Today, this observation is not considered a " classic '

... variability understood, but as a bacteriophage effect ”(<1934> 1980: 122 f.). The possibility of noticing a bacterial-dissolving and -modifying agent and its relationship to certain chemical and physical substances was certainly created, with changes in the way in which bacterial strains were created and cultivated and with the use of certain chemical and physical forces . Of particular importance was the extraction of pure cultures of lubrication plates (initially smears were obtained from mixed or lubrication cultures), which were needed, for example, to test the virulence of suspect germs. With the appropriate duration of their storage, bacterial variabilities could be set that are less visible on lubrication plates.

10). Contrary to the prevailing doctrine of bacteriologists at that time, that phages should cause a change in bacterial characteristics and the emergence of new types had to be maintained, which adhered to a rigid scheme of bacterial groups.28 That new (lysine-resistant) bacterial strains (secondary Cultures) with other morphological properties, with different fermentation capacity, fermentative behavior etc., in the course of the experiments, could develop that bacteria disappeared and recurred as a result of the action of lysine, such as, for example, colibacilli at the beginning of dysentery, cholera etc. and reappear with convalescence, "disrupted" the bacteriological practice, which aimed to to extract a well-defined microorganism from pathogenic material (for example pus) and to demonstrate the amount and distribution of the bacteria in order to interpret symptoms.29 Because the bacteriologists were primarily concerned with identifying bacteria as pathogens - for which the stability of the morphological ones Characteristics unaffected by experimental access to the cultures - they were hardly interested in variability. Findings that seemed to indicate such phenomena were therefore often attributed to the effects of technical errors.30 Identifying bacteria as pathogens - for which the stability of the morphological features had to be assumed, unaffected by experimental access to the cultures - was of little interest to them in terms of variability. Findings that seemed to indicate such phenomena were therefore often attributed to the effects of technical errors.30 Identifying bacteria as pathogens - for which the stability of the morphological features had to be assumed, unaffected by experimental access to the cultures - was of little interest to them in terms of variability. Findings that seemed to indicate such phenomena were therefore often attributed to the effects of technical errors.30

Bordet and Ciuca (1920) assumed that bacteriophage reproduction was triggered by leucocitary elements (as already mentioned above, Kabéshima 1920 also assumed that the leukocytes could cause bacterial dissolution). In order to explain the effect of this impulse, they took the inheritance concept as a help: Under the influence of a stimulus originating from (for example, masses of leukocytes in the Ruhr chair) variants would develop in the colony forms containing the lytic agent. Under the damaging influence of the cells, variants of the Ruhr bacilli were to appear which contained an autolysis-promoting substance. The autolyzing variants should be able to inherit this property. If the bacilli die, the autolytic ferment would be released, that could affect normal dysentery bacilli, which would also give them a tendency to autolysis. Gildemeister (1917) found that on stool smear plates (including Ruhr and Colibacilli) one of the two occurred in a number of cases

28 It failed "due to the resistance of nature ... which does not tolerate schematization" (Hoder 1932: 115).

29 Also, the “self-healing” hoped for by the lytic principle - the therapeutic effectiveness of the parasite that resolves the bacteria with regard to bacterial infections - could not be easily reconciled with the idea of causal therapy for infectious diseases through isolation, identification and characterization of a pathogen be. However, the expectation of many medical professionals that phages could be used successfully for targeted therapy against some infectious diseases was not fulfilled later.

30 In the "classic age of Pasteur-Koch ...", said Fleck, "a rigid bacteriological style of thinking developed: since only a strictly orthodox method was recognized, very narrow and even results were obtained. For example,

only one 24-hour repulping of the cultures was used in general, very fresh cultures, about 2-3 hours old, and very old cultures (about 6 months old) were not considered worthy of investigation. Therefore, all secondary changes in cultures, which form the starting point for variability theory in a new style, are received by the attention ”(Fleck, op. Cit., 122).

different types of bacteria in their main characteristics formed a group of peculiarly irregular colonies. In these colonies there was more or less limited growth of the bacillus. Individual forms of this group turned into one another during further breeding, and the "constantly changing clans" split off normal forms (ibid., 54). He gave vaccinations from bacterial floods, to which Gildemeister had given a bacteriophages "lysine" (as he called this phenomenon), and he received the same types of colonies (ibid., 56). He called them "flutter forms", with which he later linked the claim that he had discovered before d'Herelle that the lytic agent formed colony forms (1923: 181). After becoming aware of d'Herelle's work, he assumed

The investigations of the bacterial-dissolving phage effect, the detection of which, according to Hoder, meant "a considerable complication of bacteriology and ... a final breakthrough of their overly rigid systematics", "which, thanks to mutation research, has already ... wavered and is questionable Gaps ”(1932: 100 f.), Did not immediately lead to a unanimously accepted new theory with which the crisis situation could have been ended. That both the "d'Herellean phenomenon" (brightening of the broth cultures without visible residue) and the "Twortsche phenomenon" (a glassy material that resulted from the dissolution of coconut colonies spread on agar) would refer to the "same natural facts", was claimed by Gratia, among others (Gratia / Jaumin 1921: 880); he was able to convert one phenomenon into the other (this contradicted d'Herelle, who had initially thought that the phenomenon he had discovered was not identical to the Twortian phenomenon) .31 But this did not in any way level the Digging between the perspectives of both explorers. Rather, a controversy developed between supporters of the Tworts and supporters of the d'Herellian conception, which was to be renewed again and again with empirical advances in phage research. “The witless polemic that revolved around the Twort-d'Herellian phenomenon,” said Anderson 31 However, this in no way caused the trench to level between the perspectives of both discoverers. Rather, a controversy developed between supporters of the Tworts and supporters of the d'Herelleian view, which was to be renewed again and again with the empirical progress of phage research. “The witless polemic that revolved around the Twort-d'Herellian phenomenon,” said Anderson 31 However, this in no way caused the trench to level between the perspectives of both discoverers. Rather, a controversy developed between supporters of the Tworts and supporters of the d'Herellian conception, which was to be renewed again and again with empirical advances in phage research. “The witless polemic that revolved around the Twort-d'Herellian phenomenon,” said Anderson

31 In the early 1920s he proposed the term “bacterioclasis” to refer to Twort's phenomenon and understood it to mean fragments, tiny granules that could be colored red with Giemsa, whereas what he discovered should be called “bacteriophagis” because it was something else. So the lysis is of an extension that leaves no residue, the phenomenon extends to the whole culture, whereas the phenomenon he discovered is circular, stable plots on the culture (1923). This view was rejected by Gildemeister (1923: 182) among others. He considered the objections raised by d'Herelle against the identity of his discovery with the Twort phenomenon to be irrelevant; the phenomenon should therefore be named after Twort and d'Herelle. However, an article by Lisch (1925) published a few years later states that different strains of Bac. pyocyaneus showed two distinguishable phenomena that corresponded to the Twortian and d'Herellian phenomenon. A transition

between the two phenomena could never be observed. It gives the impression that one of the phenomena is a solution to the older individuals, the other is an inhibition of growth or division.

gaze (<1969> 1972: 72), lasted several decades and only became obsolete with the molecular genetic phage research. The results obtained were not such that they clearly spoke for or against the living nature of the phage, so that "many judgments about the nature of the bacteriophage are subjective," as Gildemeister and Herzberg found in the mid-1920s (1925: 403). The fact that the bacteriophage effect could be observed to a certain extent with the eyes - it could be identified as an inhibition of the turbidity in broth cultures or brightening of the already cloudy broth and as formation of growth-free spots in bacterial turf on agar plates - did not contribute to a generally accepted Understanding at. "Neither one nor the other way of making the bacteriophage effect visible is completely suitable," says Hoder in the mid-1920s, "to serve for bacteriophage determination" (1925: 424). Each side was able to give experimentally supported reasons for representing their position, so that when deciding for or against the living being theory “it ultimately depends on the position of the author, how he evaluates his results”, as von Gutfeld in 1925 judges (1925: 427). The thesis that bacteriophages could appear spontaneously in pure cultures was evaluated in the same way, "by the various authors depending on their attitude to the virus theory of Herelles ..." (Gildemeister / Herzberg (1925: 406). Doerr (1922: 1538) describes the situation as follows: "... between a pathogen that is only pathogenic for bacteria and microscopically invisible,

The understanding of the virus as a parasite benefited that the filterable agent only grew at the expense of living bacteria. Because the effect, which was claimed to be parasitic, could extend to several types of bacteria, it was reasonable to assume that adaptation would probably be necessary. According to Bruynoghe (1921), the virulence of the individual phage strains had to be regarded as different and passages as a possibility for increasing the virulence. According to Hoder (1932: 10), only one species or group was attacked at a time. In this case, the intensity with which the individual individuals in the group were attacked was not the same for everyone.

The emergence of germ-free spots in the bacterial lawn after a drop of bacterial suspension, which has been added with a small amount of virus, is placed on agar can be understood as colony formation of the virus, which was caused by phage proliferation. One could assume that the phage developed here at the expense of the simultaneously vaccinated bacteria. The formation of the peculiar holes that came up when one

Lysine solutions diluted with bacteria and spiked on the surface of solidified nutrient media (like "colonies" of bacteriophages) supported the argument that they could only form if germs remained at these places, which would then result from infection of the surrounding ones Bacteria would find the possibility of multiplication. In one of his experiments, d'Herelle considered that the possibility that the sterile stains, instead of indicating colonies, resulted from the fact that there were weak and therefore undevelopable bacteria in the affected areas.32

It could be shown that in the case of serial breeding of bacterial cultures, certain properties of phages obtained at different times compared to certain or different strains of bacteria are retained, in the same way that certain species characteristics are retained or properties are inherited over generations. Because of their work, D'Herelle and his followers saw an agar passage or passage in vivo as something analogous to a generation of specimens of an animal species. In vitro, only a faster generation sequence was sought (by increasing the virulence).

It was pointed out that the phage can be destroyed by chloroform and glycerin, i.e. by substances that can attack particularly living elements (other researchers again attributed glycerin resistance to all viruses; see Gildemeister 1939b: 103). Phages also proved to be very resistant to quinine. It was shown that neutral quinine salts in 1% concentration of the solution can render the bacterial dissolving agent ineffective in a few hours (in higher, 3% concentration even in 30 minutes). This was taken as evidence that the lytic principle must be a microorganism, since the quinine is probably toxic to bacteria and protozoa, but has no harmful effect on diastases and toxins (see Doerr 1922: 1537).

Evidence could be put in the field that the phage adhered to certain conditions
“Got used to” under which he had originally not been able to develop his lytic effect. For example, Prausnitz had succeeded in making phages insensitive to the neutralizing effect of their antiserum by habituation, that is, in producing anti-serum-resistant “lysines” (1923: 187). It was from an increase in resistance of the

32 This experiment can be described as follows: If increasing amounts of bacteria are added to several broth tubes and a constant dose of bacteriophage suspension is applied and, after shaking from each tube, the same amount is applied to agar, the number of spots arising from each tube is the same. However, if increasing amounts of phage are added to the same amount of bacteria, the number of spots of the amount of phage used is parallel. If each stain were caused by the fact that there was a particularly weak bacterial cell on it, the number of aseptic sites in the first test arrangement would have to correspond to the quantity of bacteria used, and the same number of sites would have arisen in the second arrangement. However, the experiment showed the opposite: from this d'Herelle concluded

Phages against the effects of antiseptics in culturing them in culture have been reported (Prausnitz 1922). Janzen and Wolff (1922) reported that the phages they obtained at different times could get used to antiseptics (achieving "poison resistance"). Asheshov announced that he had managed to get a phage used to its effects even in an acid medium, which he was originally unable to do (1925: 643 f.). And with suitable breeding conditions, the phage could gradually be made unresponsive to certain influences or a partially lost (bacteria-dissolving) effect. Such properties were only known from living beings (see von Gutfeld 1925: 426).

When comparing these reasons for accepting the d'Herellian position, it is striking that they are those which, despite their diversity, are comparable in one: they are compatible with the understanding of the phage as a living being, with the understanding, however, that you had life at the time. “It is impossible,” said von Gutfeld (ibid.), “To characterize the term 'life'. We refer to something as alive if it has the qualities that, in our experience, belong to beings that we tend to consider alive. If they are big enough, it will have no difficulty. The possibility also exists for beings below the visibility limit. However, observation alone is not enough ... One must rather examine the properties of the being in question.

But there were also plausible reasons to assume that the phenomenon was a bacterial decay product. This was supported in particular by the dependence of the bacteriophage on the metabolism of the bacteria, which, according to several researchers, could hardly be reconciled with the existence of a microbe (see Doerr 1922: 1489 f. And 1537 f .; 1923: 909 ff.). 33

33 This argument could also be used to deny viruses of any kind. To reject it, supporters of living thing theory considered, among other things, that the filterable virus could be a case of declining evolution resulting from a process in which an organism lost some functions - and smaller and got easier - is what would explain the virus' dependence on living cells. This assumption has become known as the Laidlaw Green hypothesis. It states that filterable viruses cannot reproduce autonomously because they have lost certain metabolic functions, so that they are dependent on certain growth substances available from host cells (Green 1935; Laidlaw 1938).

Bordet, who had given the phenomenon the expression "transmissible autolysis", and Ciuca (1920; 1921: 748 and 754; see also Bordet 1924: 969; von Gutfeld 1925: 428) had brought together a small amount of lysine with a large amount of bacilli and found it that the lysine did not regenerate under these conditions. They took this as evidence that the transferable lytic principle is not organized, that is, it is not a living being, but only a lifeless ferment, since despite the best nutrition there was no increase. According to Bordet and Ciuca (ibid.) There is nothing more than a bacterial variation - the product of a metabolic disorder of the bacteria. This view was also made plausible by referring to messages about

It has also been known that certain inactivated ferments can be activated. This insight could very well be related to the fact that, after initially negative results, lysine was formed again in the cultures that were prepared with heated phages (see Otto / Munter 1928: 400). According to Otto, observations on the development of such enzymes from bacterial protein provided plausible reasons for the assumption that the bacterial-resolving appearance was caused by bacteria alone (1923: 257).

There were also reports of great resistance of the “lysine” to higher temperatures that kill living organisms (on the other hand, according to d'Herelle, the bacteria-dissolving substances lost their biological effectiveness when heated to 60 ° Celsius for one hour) and that an ether treatment, which is a living being would not have survived that the bacterial-dissolving principle could not have been destroyed (see von Gutfeld 1925: 427 f.). The resistance to chemical disinfectants also spoke against the Position d'Herelles. Kabéshima concluded from the ineffectiveness of chloroform and fluorosodium on the bacteriophage that the bacteriophage should not be a living being but a ferment (1920: 471).

If, as d'Herelle assumed, phages could multiply in an extra-cellular medium, then, as was argued, they would have had to detect respiratory processes. Bronfenbrenner (1926) and other experimenters had also attempted to detect them, for which purpose a specially designed microrespirator was used, which even allowed extremely weak amounts of carbonic acid to be registered. But even after several days of use, no traces of CO were found in the filtrate. This failure, however, could still be explained at the time by reference to inadequacies in the design of experimental conditions, so that the results, Seiffert (1938: 7), should not yet be regarded as final in their results. It should be added

believed from what they concluded that the vaccine causative agent must be a living being (1935: 1149). Although these findings did not seem to be certain to other researchers (Seiffert 1938: 7), they nurtured the idea that one day breathing processes could also be demonstrated in phages.

Werthemann found that "intravenously injected lysine in guinea pigs, rabbits and frogs disappears from the circulation according to the laws determined for colloidally dissolved protein bodies, but not suddenly, critically", as is otherwise the case with ultra-microbes "(1922: 255).

Z.UR ERESEARCH OF THE VIRUS AS A TUMOR GENERATOR AGENS

However, there were very different views on the nature of the "cancer virus". A number of researchers saw an allegedly cell-free tumor filtrate as an endogenous element that subsequently increased auto-catalytically and intracellularly. Other researchers saw the agent as an exogenous agent. A concept that attributes the development of tumors to virus-like agents did not oblige the process to be regarded as an exogenous infection. Even researchers who rejected the concept of an exogenous pathogen of cell-free sarcomas or other cancer growths and instead thought of a substance that is produced in the host organism believed in the viral nature of cancer-causing agents, although the question of how the tumor virus is in an organism educates could not yet answer (see, inter alia, Doerr 1938; Graffi 1940) .34 They considered the cell to be the origin of the virus, which, however, can be transmitted through cell-free filtrates. The majority of cancer researchers, of course, rejected both the one and the other variant of the virus concept, namely

34 However, there were also individual researchers who identified the virus as an exogenous pathogen and therefore refused to give it a role in cancer. For example, for Murphy, who believed that he had produced filterable tumors from chicken germ cells, tumorigenic agents were something that would differ fundamentally from the virus types because tumors were endogenous and were due to the effectiveness of an endogenous chemical substance (1935; Note from: Seiffert 1938: 9). He compared the agent causing poultry tumors with the transforming principle of pneumococci. He called these two groups of agents "transferable mutagens".

Convinced that all the phenomena of cancer growth were due to the spread of cancer cells, that the cancer problem was a regulatory problem of cellular processes in the organism. 35

In a sense, the search for filterable agents followed the direction in cancer research where the formation of malignant tumors was considered an infectious disease caused by parasites that needed to be cleared up, combined with the notion that therapies could be developed that turn against a pathogen instead of the tumor cells. The fact that an animated agent would cause cancer was mainly accepted by clinicians and doctors. It was considered whether certain worms (nematodes, see Fibiger 1921), blastomycetes (Roncali 1914; Pentimalli 1916) 36, cockroach larvae, mites (Saul; note from: Teutschlaender 1927: 231; without source), protozoa (van Calcar; reference from: Teutschlaender 1927: 225; without source), certain strains of bacteria (Blumenthal 1918; Reichert 1925) or other organisms that cause tumors. And since bacteriology has existed, attempts have been made time and time again to identify specific cancer pathogens in accordance with Koch's postulates. The reports of alleged cancer or sarcomere pathogens were sometimes linked to the claim to have discovered the sole "universal pathogen". 37

The idea of "injecting cell-free cancer juice" to track down the growth of the tumor

35 A special hypothesis for endogenous cancer formation was put forward by O.Warburg (1926). He considered cancer to be the result of irreversible damage to cellular respiration. He examined the metabolism of tumor cells in comparison to normal cells and found significant differences. While normal cells obtain the energies necessary for life through breathing alone, malignant cells show yet another source of strength for their existence, namely the ability to stay alive even with complete depletion of oxygen, through the fermentation of sugar to lactic acid . Cancer cells have an increased sugar consumption, so the blood that has flowed through the tumors is richer in lactic acid than the blood that flows into them. Normal tissues don't ferment because their breathing is so big that sugar fermentation to lactic acid is suppressed in the cell. Breathing produces orderly growth in all growing cells. In cancer, however, breathing and fermentation cause the disorderly malignant growth. Only when there is a lack of oxygen also normal cells form lactic acid from sugar. In the tumor cells, however, breathing is usually not large enough to suppress sugar fermentation. All toxins and damage that artificially damage normal respiratory cells change these cells so that they ultimately deny their life energy primarily from sugar fermentation. So the cancer problem would ultimately be a metabolic problem. In cancer, however, breathing and fermentation cause the disorderly malignant growth. Only when there is a lack of oxygen also normal cells form lactic acid from sugar. In the tumor cells, however, breathing is usually not large enough to suppress sugar fermentation. All toxins and damage that artificially damage normal respiratory cells change these cells so that they ultimately deny their life energy primarily from sugar fermentation. So the cancer problem would ultimately be a metabolic problem. In cancer, however, breathing and fermentation cause the disorderly malignant growth. Only when there is a lack of oxygen also normal cells form lactic acid from sugar. In the tumor cells, however, breathing is usually not large enough to suppress sugar fermentation. All toxins and damage that artificially damage normal respiratory cells change these cells so that they ultimately deny their life energy primarily from sugar fermentation. So the cancer problem would ultimately be a metabolic problem. that they ultimately deny their life energy primarily from sugar fermentation. So the cancer problem would ultimately be a metabolic problem. that they ultimately deny their life energy primarily from sugar fermentation. So the cancer problem would ultimately be a metabolic problem.

36 "Blastomycetes" are unicellular fungi that multiply through sprouting.

37 Ochsner described the streptococcus discovered by Nuzum in 1919 as "the ultimate cause of cancer". He was able to regularly isolate the micrococus from human breast cancers and to produce carcinoma by repeated injections of pure cultures in mice and a dog. Ochsner reported similar successes with the same micro coccus. In 1921, Glover announced the discovery of a microorganism that was said to have been bred not only from breast, but also from bladder, uterus, lip, and liver tumors, even from lymph nodes from cancer patients and also from mouse tumors. Van Calcar saw the cause of cancer in a protozoon (information from:

Teutschlaender 1927: 225, 240 f .; without source). According to Teutschlaender, tissue changes were often given as cancer formation regardless of their histological behavior,

was pronounced by Lubarsch as early as 1902 (reference from: Teutschlaender 1927: 242; without citing the source). After Lewin (1925: 456 f.) Borrel (1909) was probably the first to discuss the etiological significance of an invisible virus for the question of the development of the tumor. However, he had not come to a positive result experimentally. As the earliest evidence of the viral nature of cancer, Wunderlich and Uckert (1984: 7) cite Ellermann and Bang in 1908 as successful cell-free transmission of chicken leukosis (see also Ellermann 1918) .38

Observations that Rous had begun in 1909 proved to be particularly important for the further development of this research direction. He reported that during his experiments he had found that chicken sarcoma could be transmitted with filtrates (1911a; full text reproduced in: Lechevalier / Solotorovsky 1965: 198 f.). In his first experiments, ordinary filter paper was used, assuming that the thin layer of paper, which allowed red blood cells and lymphocytes to pass through, would hold back the tumor, so that a harmless filtrate should result. especially since other researchers who had observed mouse and dog tumors believed that the filtrate was sterile. But Rous found that there was tumor growth, if one injected some of the aqueous filtrate from his chickens used for his experiments, for which a few drops were sufficient. Even when he used the clear liquid above the sediment to vaccinate after centrifugation of the tumor, he came to this result, which prompted him to try again: Rous ground sand from the chickens with chicken, added Ringer's solution and It shook mechanically for a while (20 minutes). The sand and the tumor pieces were then centrifuged out over a period of 5 minutes (at a rotation speed of 2800 per minute). The supernatant liquid was then removed with a pipette, which in turn was centrifuged (at 3000 revolutions per minute) for a quarter of an hour. Sufficient fluid was then removed from the upper layers for vaccination and injected into one of the chicken breast sides (0.2 cm3 each), while a small piece of tumor tissue was injected into the other side. With the tumor pieces, Rous achieved positive results in all (92) chickens, while in some specimens (7) sarcoma development could also be achieved with the filtrate. In a further experiment (see Rous 1911b) the liquid was passed through Berkefeld filters after centrifugation. Nine chickens were injected with 0.2 cm3 of the filtrate in each breast side, 22 chickens only in one side, while a little tumor tissue was added to the other side. In one of the 9 chickens, sarcoma gradually developed on each side. And at while a small piece of tumor tissue was injected into the other side. With the tumor pieces, Rous achieved positive results in all (92) chickens, while in some specimens (7) sarcoma development could also be achieved with the filtrate. In a further experiment (see Rous 1911b) the liquid was passed through Berkefeld filters after centrifugation. Nine chickens were injected with 0.2 cm3 of the filtrate in each breast side, 22 chickens only in one side, while a little tumor tissue was added to the other side. In one of the 9 chickens, sarcoma gradually developed on each side. And at while a small piece of tumor tissue was injected into the other side. With the tumor pieces, Rous achieved positive results in all (92) chickens,

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38 These experiments, according to von Hansemann, "proved ... that chicken leukosis is an infectious disease ... (and) a communicable disease" (von Hansemann 1919: 472 f.).

5 of the 22 chickens who had been injected with both filtrate and tumor fragments also showed sarcoma development on each breast side, the process taking place particularly quickly at the site injected with tumor tissue.

Rous considered the results of his experiments, which had been neglected by the scientific community for a long time (see Studer / Chubin 1980; note from: Fujimura 1996: 32), as evidence that after filtering a tumor emulsion and inoculating the filtrate can produce a tumor of the same type in the chest muscles of a healthy chicken on the same. Rous was able to refer to some characteristics of this agent which supported the understanding that it was a living but extremely small microbe. This was supported by the fact that saturation with chloroform abolished the virulence of the material. The agent was also destroyed at a temperature of 55 ° Celsius in a relatively short time (15 minutes). About the nature of cell-free filtrate from a chicken sarcoma, With which sarcomas could be produced on other chickens, Rous was not yet conclusive. There was no proof of the vitality of the agent, one would have had to show that it can be grown outside the body. But Rous saw no good reason to assume that the natural occurrence of chicken tumors was due to an exogenous infection.

Among the researchers who, despite the fact that the cultivation problem was still waiting for a solution, found that they had come across a cancer virus in their experiments included Keysser, who even claimed to be the result of experiments with mouse tumors earlier and independently of Rous to have determined that it was not carcinoma cells but a filterable virus that was the tumor-causing agent (1913: 1665). Keysser started from the question of whether “tumors growing infiltrating in mice can be achieved experimentally, which can be regarded as equivalent to human tumors” (ibid., 1664). However, in order to achieve infiltrative growth of the tumors, he considered it necessary to vaccinate organs instead of continuing the “previously performed subcutaneous transfer by transplanting pieces of tissue or injecting undiluted, crushed tumor porridge”. As a result of this method, the subcutaneous tumors appeared as foreign objects in the mouse, which were not similar to human tumors. He regarded the eye as a particularly suitable organ for his experiments, following the idea “that it may be protective substances in the blood and juices that prevent the tumors from being attacked. Now we have in our mind a self-contained organism that we know that there are no or only small amounts of protective substances in the vitreous fluids as well as in the anterior chamber, that the proteins contained in the eye belong to the lower and belong to simple types of protein, who have no specificity ”(ibid.). To an eye (or other organ) as indicated

In his opinion, the use of a method was necessary to avoid gross injuries to the experimental animals that overlap the intended experimental effect, such as would have to be accepted when transplanting tissue pieces or injection with undiluted tumor pulp. He therefore carried out the vaccination with the thinnest possible suspensions from subcutaneous mouse tumors, which were penetrated by hair-fine cannulas. According to his report, vaccination of just one or two drops of this thin emulsion in the organs already led to the formation of tumors. Tumors vaccinated in this way grew after 8 to 14 days and reached hazelnut to walnut size in 4 to 6 weeks. All the organs were completely penetrated by the tumor.

Keysser also went on to attempt transmission of spontaneous mouse tumors and human tumors to rats. When vaccinated into the eye, macroscopically visible tumors could be caused. They could also be obtained from rat spleen vaccinations. In one case, this also succeeded when the testicles were vaccinated. In these new growths, cell complexes were found that had cells of the same type as the parent tumor. Keysser also considered the occurrence of necrotic (dead) masses with small cell infiltration to be characteristic of the development of organ tumors in mice originating from mice. "... we therefore have the same microscopic picture of the tumors that have been developed that are foreign to the species that are available in mice when vaccinated with organ tumors" (ibid., 1665). The further vaccination of the tumors obtained in rats, originating from mice and humans, succeeded in only one or two passages. And vaccinations on alien animals only came in 5%. Keysser explained this in such a way that when planning the heterologous tumors, one still has to count on as yet unknown dispositional moments, which for the time being can only be ruled out by establishing large series of vaccinations.

Since the vaccination of organs with such thin and extremely small amounts of tumor juice helped to initiate tumor development, Keysser considered it reasonable to assume that the cancer cells might not be of any importance for the further vaccination. In order to check this, he switched to experiments with inoculum that he wanted to have made cell-free by centrifugation. He inoculated organs several times with ascites from mice (with a fluid that accumulates in the free abdominal cavity when suffering from abdominal fluid), which had formed in these as a result of a large liver tumor. It was possible to achieve tumor formation in organs with the clear substance centrifuged out of liquefied tumors. These findings

in his opinion, argued that in a material in which macroscopically no cancer cells are present and with which successful vaccinations can be carried out, there must be virus that is able to produce new tumors independently of cancer cells . In order to substantiate this assumption, he extended the vaccination attempts in a certain direction. He produced filtrates from mouse tumors (using a porcelain filter) and used them to inoculate the animals into organs. He succeeded in obtaining a macroscopically visible tumor in the eye of a rat and in proving that a tumor had developed from the filtrate that corresponded pathologically and anatomically to the original tumor from which the filtrate was made.

Henke and Schwarz (1914) also reported a little later that mouse carcinoma can be transmitted through filtered starting material. For this they used a very virulent carcinoma strain. In addition to several failed attempts, they were able to achieve a positive result in 8 cases with 8 vaccinated mice. These animals had been vaccinated with a filtrate prepared as follows: After grinding two living mice from tumors removed with quartz sand, a largely homogeneous emulsion was suspended with 6 cm3 of saline solution and centrifuged for a long time. The fairly clear liquid above the sediment was then filtered to achieve cell freedom. After that, cells could no longer be identified microscopically. Henke and Schwarz were led to suspect that that there might have been pathogens in the filtrate that would have reproduced the tumor in the new animal body. The newly formed tumors had formed themselves at the vaccination site. At the same time, Fujinami and Inamoto (1914) described a myxosarcoma with whose filtrate the same tumor could be formed by vaccination. In the same way, other sarcomas could be vaccinated on chickens. Morris (1917) had been able to create new tumors in about 3000 rats and mice by filtrating tumors, tumors which, however, differed significantly from the initial tumor histologically. Some of these animals developed gland carcinomas, some of which showed slimy degeneration. Morris also assumed that an invisible virus was the cause of the tumor development. A similar view was taken by Teutschlaender (1920) with regard to chicken sarcomas (later he moved away - see Teutschlaender 1925). According to his information, positive tumor inoculations could be achieved with filtered tumor juice, with dried tumor powder and with tumor cells stored in glycerine for weeks.

The idea that viruses could cause cancer was also from a different direction

cancer research emerged from transplantation biology, which had gained weight in the early 20th century, a direction in which the question of whether tumors from one animal to another was could create sultry or not. The researchers were interested in cancer susceptibility and the development of specific types of cancer, and in this connection thought about inheritance and transmission, so that it was necessary to uncover genetic factors that could be involved in tumor etiology. The question arose, among other things, because there have been results from experiments in which tumors of rats and mice could only be transplanted onto animals of the same type. So it was necessary to check whether the tendency to tumors is a problem of genetic control or not. Here it was obvious to include experimental animals with a largely identical genetic composition in the investigations. To make this possible, inbred lines of mice (later also rats and guinea pigs) were created by sibling mating over several generations in the 1920s. Genetically, inbreeding means the multiplication of homozygous (homozygous) and the diminution of heterozygous (mixed genes) gene pairs. The populations of highly homozygous individuals also tended to develop the same types and structures of tumors. Two types were created, one with a strong and one with a weak tendency to develop breast tumors. Individuals of the first were then crossed with individuals of the second type. After the cross-breeding experiments, however, it was found that only offspring of dams from the group suffering from breast tumors again developed tumors. However, if male animals from this group were included in the experiment, the offspring remained free of tumors. This result contradicted the thesis of the genetic inheritance of the tumors: Gender could not play a role in genetically controlled tumor formation, since males and females had the same genotype. The idea came up that the cancer was caused by a virus that was passed on from the mother to the offspring when nursing (see Bittner 1936 and 1942). However, if male animals from this group were included in the experiment, the offspring remained free of tumors. This result contradicted the thesis of the genetic inheritance of the tumors: Gender could not play a role in genetically controlled tumor formation, since males and females had the same genotype. The idea came up that the cancer was caused by a virus that was passed on from the mother to the offspring when nursing (see Bittner 1936 and 1942). However, if male animals from this group were included in the experiment, the offspring remained free of tumors. This result contradicted the thesis of the genetic inheritance of the tumors: Gender could not play a role in genetically controlled tumor formation, since males and females had the same genotype. The idea came up that the cancer was caused by a virus that was passed on from the mother to the offspring when nursing (see Bittner 1936 and 1942).

In the mid-1920s, the difficulties that could only be assumed to exist before the existence of cancer-causing viruses - difficulties that had arisen in the visualization of tumor-inducing agents and in the attempts to breed them - finally seemed to have been eliminated . The sensational announcement, celebrated in the British press as a turning point in cancer research, came from Great Britain39 that it was possible to photograph something that caused

the tumor in ultraviolet light. Barnard (1925), who had developed the technical conditions for this40, believed it to be from other similar bodies as found in most organic ones

39 Teutschlaender (1927: 251) was primarily responsible for the sensationalism in the daily press that caused the sensation that the work of Gyes and Barnard had caused in public at the time, and he feared that this could spread an unfounded fear of contagion and fear of cancer.

Find liquids to be able to differentiate after attempts to visualize them using various staining techniques have failed. It was possible to identify granules on wafer-thin layers of tissue with the dyeing, but, according to a number of researchers, these could not be the viruses sought. "The films," says Gye, "showed innumerable pink granules on the border-line of resolution. Such experiences as these have led me to the opinion that such granules are not the virus. The visual discovery of such small organisms is obviously a special problem in optics "(Gye 1925: 114).

The messages were also of sensational importance because they brought to light successful cultivation attempts. Gye (1925) reported that it was now possible to grow the agent of the chicken sarcomas first described by Rous (with the addition of rabbit serum) in vitro, that the filterable causative agent of the cancer spreads from culture to culture in certain composite nutrient media. He had started out from Rous's discovery that filtrates and extracts from powdered swollen chickens, which should no longer contain living cells, were injected into healthy chickens and produced sarcoma-like swellings. Gye was able to increase the amount of the agent from the chicken tumor enormously if he brought pieces of the tumor into broth, which he used potassium chloride, rabbit serum and often added sugar. A fragment from a 12-16 day old chicken embryo was added to such a broth. The whole was kept anaerobically at 35 ° and 36 ° Celsius. A drop of the first culture was placed in this mixture. If a small amount of such a subculture was repeatedly brought to new culture medium, despite the eventual dilution of the starting material down to a trillionth, the tumor could be produced again by inoculating a healthy chicken with the liquid obtained. In another experiment, Gye placed bits of various mouse and rat tumors in the culture fluid described above, made subcultures that were kept anaerobic, and vaccinated chickens with them. The results were negative. He then mixed the culture with kieselguhr and filtrate from chicken sarcoma that had been treated with chloroform. With this mixture, he was able to produce tumors in chickens that showed the same structure as Rous's tumors. From this he concluded that he had multiplied the same virus from mouse and rat carcinomas and sarcomas that was the causative agent of the swollen chicken.

Gye had found that the agent under investigation lost its effectiveness after a number of culture passages, that is to say that the tumor vaccine yield became less and less. That it was possible to produce typical Roussarcomas was therefore just as easily attributable to the transfer of a chemical substance such as a filterable living agent.

40 Barnard had already been developing microscopic techniques for the visualization of filterable infectious agents from 1916 onwards (see Barnard 1939: 3f.).

The results of metered filtrate vaccinations, which showed that the effectiveness of the filtrates increases or decreases with their quantity, seemed to speak for the former variant. When vaccinated with 1 cm3 of pure filtrate, a palpable tumor developed after only 2 weeks, while when vaccinated at 0.5 cm3 the tumor was only about the same size after 3 weeks and when vaccinated at 0.25 cm3 after 4 weeks. With an even smaller amount, tumor formation did not occur. In contrast, there was evidence for a revitalized agent that the virulence of the "primary cultures" that had been obtained in the attempts to first grow the tumor in broth containing potassium chloride only after 48 hours, with the addition of rabbit serum or under anaerobic conditions, only after a week, which is slower than lost in the absence of serum or the presence of oxygen. Gye now came to the explanation of the decreasing effectiveness of the material on the idea that this phenomenon is not due to the death of the virus, but to the disappearance of a chemical substance originally contained in the primary cultures and originating from the tumor cells, the presence of which makes the infection that healthy cells depend on the virus when vaccinated (Gye 1925: 116). Certain chemical substances contained in the tumor tissue were necessary to maintain the virulence of the filterable pathogen. Neither sterilized filtrate alone nor virus alone is able to produce tumors. "Neither of these factors operating alone will cause the formation of a sarcoma" (ibid., 113). The chicken tumors would be transmitted by an animated, reproductive virus,

In order to regenerate the agent, it had to be - in line with this thesis - to add the material in question to culture again. Fresh tumor filtrate, in which the pathogens had been killed by adding chloroform, was mixed with such cultures which had become ineffective, and this mixture of propagated pathogens and effective but killed extract substance again gave full vaccine yields. The subcultures which contained the virus in question which was reproduced therein were in themselves ineffective, that is to say they produced, injected chickens, not a tumor. They only became effective if, in addition to diatomaceous earth, the filtrate pretreated with chloroform was added to them after the chloroform had been expelled again. In contrast, the experiments described do not succeed in the case of rat and mouse tumors. Gye suspected that the active chemical substance was apparently contained in too small amounts. However, with mixtures of cultured virus from rat and mouse tumors and the effective chemical factor from chicken tumors, he was able to induce chick sarcoma tumors in chickens. "This shows," as Lehmann (1926: 226) concluded, "that the same virus is present in all other malignant tumors, but the active chemical substance is specific to each animal species and

must be for every type of tumor. ” With the introduction of such a species- and tissue-specific factor, it could be taken into account that only the animal species and the tissue from which the tumor extract originated could be made infectious with the agent (otherwise there would be at least one group for each species of viruses and a specific virus for each tissue; see Gye 1925: 110).

At a cancer conference in Düsseldorf in September 1927, Blumenthal et al. reported that they had succeeded in several cases "with the injection of spleen porridge from tumor rats, in which no metastases could be detected, to produce tumors in other healthy rats, which apparently differed from the injected tumors in their histology. gave way. It was assumed that in these experiments a transmitted cancer cell could not be the cause of the newly formed tumor, rather we believed that a cancer agent with the spleen porridge was transmitted in these cases ”(Blumenthal et al. 1927: 229; see also Blu- menthal 1925: 1306). There were also messages about that a number of bacterial strains could be isolated from malignant human tumors and from the malignant tumor of the dog (see Blumenthal 1925), some of which have the ability to produce malignant tumors in rats. Reichert (1925: 449) saw in the fact that these are bacteriologically very different germs for tumor formation, the expression that “the bacteria are attached to the tumor by an ultravisible virus, which is the real one Tumors must apply. ”41 At the beginning of the 1930s, Shope (1932, 1933) reported that rabbit papilloma (a villus tumor) could also be successfully transmitted through cell-free filtered tumor juice. In 1936, Bittner attributed mouse breast cancer to a filterable agent. 42 some of which have the ability to produce malignant tumors in rats. Reichert (1925: 449) saw in the fact that these are bacteriologically very different germs for tumor formation, the expression that “the bacteria are attached to the tumor by an ultravisible virus, which is the real one Tumors must apply. ”41 At the beginning of the 1930s, Shope (1932, 1933) reported that rabbit papilloma (a villus tumor) could also be successfully transmitted through cell-free filtered tumor juice. In 1936, Bittner attributed mouse breast cancer to a filterable agent. 42 some of which have the ability to produce malignant tumors in rats. Reichert (1925: 449) saw in the fact that these are bacteriologically very different germs for tumor formation, the expression that “the bacteria are attached to the tumor by an ultravisible virus, which is the real one Tumors must apply. ”41 At the beginning of the 1930s, Shope (1932, 1933) reported that rabbit papilloma (a villus tumor) could also be successfully transmitted through cell-free filtered tumor juice. In 1936, Bittner attributed mouse breast cancer to a filterable agent. 42 some of which have the ability to produce malignant tumors in rats. Reichert (1925: 449) saw in the fact that these are bacteriologically very different germs for tumor formation, the expression that “the bacteria are attached to the tumor by an ultravisible virus, which is the real one Tumors must apply. ”41 At the beginning of the 1930s, Shope (1932, 1933) reported that rabbit papilloma (a villus tumor) could also be successfully transmitted through cell-free filtered tumor juice. In 1936, Bittner attributed mouse breast cancer to a filterable agent. 42 that these are bacteriologically very different germs for tumor formation, the expression that “the bacteria are attached to an ultravisible virus originating from the tumor, which has to be regarded as the actual tumor agent.” 41 Early 1930s Shope (1932, 1933) reported that rabbit papilloma (a villus tumor) could also be successfully transferred through tumor juice filtered without cells. In 1936, Bittner attributed mouse breast cancer to a filterable agent. 42 that these are bacteriologically very different germs for tumor formation, the expression that “the bacteria

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The claim that experimental transmissions of carcinoma filtrates with the effect of new cancer growth in previously healthy organisms were successful, the idea that malignant tumors in the animal were cell-free, which suggested a virus-induced conversion of normal to malignant cells, was in the In the 1920s, there was fierce resistance from those researchers who shared the traditional belief that cancer cells living alone are capable of transmitting the tumor to other animals (see Darányi 1937: 1267). The transferability of the transplantable animal tumors should be linked to the presence of the intact cells in the vaccine fluid. This understanding corresponded to the cell theory or cellular pathology represented by Virchow,

41 Borrel (1909) had previously put forward the thesis that higher ectoparas and entoparasites could be considered as carriers of an as yet unknown, invisible virus and that hair follicle mites played a particularly important role in the development of breast cancer.

42 In the early 1950s, such a connection was also discovered with regard to mouse leukemia (Gross 1951).

the disease af- terwards progressing independently; the other assumes that cancer is due to the continuous action of some persisting cause, such for example as a living virus. It will be seen that the two theories are mutually incompatible ”(1931: 501, quoted from van Helvoort 1994b: 138).

The researchers who resisted the infectious theory of malignant tumors included the Norwegian researchers Margit and Magnus Haaland (1927). They reviewed Gyes' attempts to use centrifuged cell-free meat broth containing pieces of tumor to inoculate tumors on mice. Cells were also inoculated for comparison purposes. Suitable liquid nutrient media (meat broth with the addition of animal protein) were charged with sterile tumor material (pieces of mouse tumors with part of the organ in question), partly aerobic, partly anaerobic (by pumping out the air and introducing hydrogen into some reagents). glasses) incubated. The vaccination was done separately, both with the pipetted clear supernatant liquid - which according to Gye should be infectious - as well as with the sediment which contained the remains of the vaccinated tumor. In a total of 168 vaccinations with the clear liquid, Haaland and Haaland could in no case cause tumor growth in mice. The

43 However, Virchow himself was not averse to the assumption of an infectious etiology of malignant tumors: “The detection of parasitic microorganisms in diseased parts, which has been increasing in number for a number of years, has aroused the increasingly optimistic hope that many will, too have a cancer bacillus found. So far, the results of even the most eager research have not been presented in a convincing demonstration. However, the possibility of such an occurrence cannot simply be dismissed; yes, it can be conceded that finding a specific bacillus would make an important step forward in the diagnosis and prognosis of carcinoma. The attempt, All the phenomena of cancer growth up to dissemination and metastasis due to the spread of cancer cells are in no way supported by anatomical and experimental findings so surely that there is no room for another mode of explanation. Conversely, the need for a cancer bacillus is not so great that without it we would be deprived of any possibility of understanding. Animal or human cells, like bacteria, have the ability to act on the metabolism and to produce effective secret substances of various kinds ”(Virchow 1888: 18). Conversely, the need for a cancer bacillus is not so great that without it we would be deprived of any possibility of understanding. Animal or human cells, like bacteria, have the ability to act on the metabolism and to produce effective secret substances of various kinds ”(Virchow 1888: 18). Conversely, the need for a cancer bacillus is not so great that without it we would be deprived of any possibility of understanding. Animal or human cells, like bacteria, have the ability to act on the metabolism and to produce effective secret substances of various kinds ”(Virchow 1888: 18).

44 Jordan considered in 1939 that the contrast between the two concepts could be removed: "Since serological experience has shown a relationship between the viruses of poultry tumors and components of normal chicken cells, it is obvious that between the two competing interpretations of the cancer problem, Mutation theory and virus theory to consider a synthesis in the sense of exploiting the similarities of virus elements and genes ”(1939: 12).

Inoculation of the tumor fragment after 24 hours of anaerobic incubation was positive in 7% of the cases, after an equally long aerobic incubation in 11%. Vaccination of the fresh tumor had a positive result in 95%. These tumors also grew faster than those obtained from the non-incubated material, which the two researchers attributed to the fact that the incubation had damaged the cells; they would partially dissolve, which could be determined microscopically. However, it should definitely be expected that the surviving cells - including the anaerobically incubated tubes - would transmit the tumor. Where these were missing, as in the clear supernatant culture fluid, there was a successful tumor vaccination also not possible. That they could only transmit the tumor

The cell-oriented interpretation of the disease could still be maintained regardless of those transmission attempts to explain the filterable, "cell-parasitic" virus. On the one hand, it could be argued that the pathological anatomy had not found any parasites on microscopic examination (see Pentimalli 1927: 348) 45, that there was no clinical evidence of the effective presence of a specific microorganism and its transferability, for example, from person to person and thus the vaccinability of the disease caused by him was present. Ideas to blame parasites for the formation of tumors have always been rejected: researchers who believed that they had microscoped protozoa, nematode eggs, mites or something other than pathogens causing certain tumors were countered, in reality they would have encountered cork cells, canvas fibers or other particles (see Teutschlaender 1927: 230 f.). Or what researchers who understood cancer as an infectious disease to be the cause of it was reinterpreted in a cell-theoretical sense: what was given out as bacteria could be understood as secondary elements that penetrated the tumors or that in the carcinoma cells seen protozoa and blastomycetes as degeneration products of a granular nature in the nucleus and cell body (see Roncali 1914: 152), as regression products of the living cell substance or as atypical cell division, discovered in carcinomas and discovered on

45 However, the question here was whether such methods were suitable at all. “The problem of the relationships between disturbed regenerative processes and tumor formation is a biological problem, which, in my opinion, histological methods have so far proven to be practically inadequate, since such methods can never teach us what happens, and how and why it happens when a regenerative element changes into a neoplastic, malignant element. The cell physiological methods, especially the energy-supplying chemical reactions, which have been elaborated in recent years and successfully applied to the carcinoma problem, are closer to the goal ”, as Pentimalli explains (1927: 348).

ne parasite-traced “cell inclusions” can be understood as degenerate leukocytes, as regressive metamorphosis (see von Leyden 1904: 308 f.) or as a secretion of hyaline (glassy solidified) substances of the protoplasm (see Honda 1903).

On the other hand, the concept of an infectious development of malignant tumors has been vulnerable for as long as the great difficulty in overcoming a cancer agent outside the tumor has been overcome. In the understanding of cancer as an infectious disease according to Koch's postulates, it was not possible to separate an active tumorigenic agent from the tumor cell, to completely isolate the parasite from the host body and to re-cultivate it sufficiently often in pure culture, thus generating cancer again. And this explains to an essential part "why the dogma could be maintained so long that only the intact cancer cell in the mammalian cancers is able to produce tumors again," says Blumenthal et al. (1927: 231). Researchers were always able to come up with findings of which they believed that they had demonstrated the effect of cell or nucleus residues in the filtrates claimed to be cell-free (see Lewin 1925: 455; see also 1928: 466 ff.). Claims by tumor researchers that they could have ruled out the presence of cells in the experiment could be questioned with reference to inadequacies in the means used for filtering, pulverizing the tumor material or other techniques. With reference to some experiments, it could be reasonably assumed that cell transfers could still occur with the effective filtrates - even when using filtration techniques that had proven themselves to be particularly useful.46 Jung reported in 1924 that at least cell debris in the filtrate, Cores with fragments of plasma still attached. And Teutschländer a little later (1925), that there were still a few cells or at least cell debris and germs in the filtrates or the tumor powder, the production of which was supposed to dissolve all cell groups. The theory that the development of cancer should depend on cells was also supported by experiments, the results of which suggested that the tumor formation was delayed with the decrease in cell material in the vaccine fluid, or the uncertainty increased that it would occur . And it was also reported time and again that only negative results could be achieved with cell-free filtrates. Loeb said that in his studies of rat sarcoma he had not been able to achieve tumor formation by switching off tumor cells by filtration, while control attempts were always positive. After all experiments, “it can be excluded with high probability that any cell outside of a cell that is viable and filtered through Berkefeld filters

46 Teutschlaender asserted that "anyone who knows about these things has had the experience that quite substantial amounts of cancer cells in the form of tumor porridge have to be injected in order to induce the formation of tumors ..." New observations have been successful To get “real tumors 3 times after subcutaneous injection with spleen porridge, 2 of which could be grown by transplantation” (ibid., 229).

hard microorganism is the cause of these sarcomas ... ”(1903: 352 f.). Königsfeld and Prausnitz (1914), who had experimented with mouse tumors, came to the same result; they, too, could never observe tumor formation when using Berkefeld filters. Haaland and Haaland (1927) also believed to have proven the ineffectiveness of cell-free material (see above).

To support the idea that the filterable agent of tumors such as chicken tumors could originate from the tissues of the tumor-bearing animals themselves, reference was made to the pronounced tissue specificity of the transmission. According to Teutschlaender (1927: 247), with the idea that it is a self-sufficient, autonomous agent, the pathogens must be assumed to be ubiquitous, which is "the best proof of the weakness of the infection theory".
“This embarrassment hypothesis seems all the more absurd to us because we don't need it at all if we don't see the specific moment of cancer development in an external factor, but in a specific factor in the body itself, which is already in every organism exists in any form or can be formed. "

It was not unlikely that the tumor formation was due to a ferment in the filtrates or to toxins.47 When chemical analysis of the Stanley Stanley virus in 1935 succeeded in isolating a crystalline protein with the properties of the tobacco mosaic virus, the suspicion was strengthened that it the virus was an autocatalytic protein, an assumption that also related to the nature of cancer viruses. Fuchs, who had attempted to detect the agent of a cancer using the same methods used by Stanley, reported at a microbiologist meeting in London in 1936 that he had obtained a crystalline substance from cell-free extract from a rabbit carcinoma, with which he can again produce histologically similar tumors in rabbits (note from: Seiffert 1938: 28; without source). It should be added that several decades earlier there had been indications that such a substance can be obtained from tumors. An article by Novell (1913: 682) states that carcinomas of humans have been used to isolate a chemical, crystalline substance which is characteristic of the tumor and which leads to multiple cancer formation in a rabbit after vaccination. Novell had made extracts from carcinoma tissue, from which he believed he could have obtained the crystalline substance by concentrating on the water bath and shaking out ether. However, this information was questioned by other researchers, such as von Fränkel and Klein in 1916.48. An article by Novell (1913: 682) states that carcinomas of humans have been used to isolate a chemical, crystalline substance which is characteristic of the tumor and which leads to multiple cancer formation in a rabbit after vaccination. Novell had made extracts from carcinoma tissue, from which he believed he could have obtained the crystalline substance by concentrating on the water bath and shaking out ether. However, this information was questioned by other researchers, such as von Fränkel and Klein in 1916.48. An article by Novell (1913: 682) states that carcinomas of humans have been used to isolate a chemical, crystalline substance which is characteristic of the tumor and which leads to multiple cancer formation in a rabbit after vaccination. Novell had made extracts from carcinoma tissue, from which he believed he could have obtained the crystalline substance by

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47 According to Lewin (1925: 455), in the course of time some tumors were removed from the group of malignant tumors as undoubtedly toxic-infectious.

48 They expressed their doubts in an essay in the Journal of Cancer Research, Vol. 15, 1916 (reference from: Lewin 1925: 463; without title).

Another reason for an endogenous specific factor was that cancer reactions cannot be equated with common reactions against infectious agents. The malignant tumors, unlike the changes in infectious diseases, could not be seen as defenses against external stimuli. For Doerr, it was proven that an exogenous infection as a specific cause of development, such as the spontaneously occurring, cell-free transferable chicken sarcoma, did not exist (1938: 45 ff.). Cancer formations, according to Teutschlaender (1927: 247, 248), impressed as more or less derailed tissue formations that were caused by specific external factors, be they parasitic or non-parasitic in nature (for example, it was possible to regularly produce cancer with tar and pitch) 49 , would only be triggered.

However, one could object to the idea of an endogenous chemical substance as a tumor that, among other things, that in the case of chicken tumors, vaccination with filtrates from cell emulsions hardly results in a much worse vaccination result than the transmission of the cell pulp that is usually used for vaccination, even though it does the filtrates should not be cell-free, there could only be very few cells in them (see Lewin 1925: 461). For the fact that it is not the cell of the tumor, but rather the virus that causes the tumor to be vaccinated, it could also be stated, for example, that ultraviolet light kills the cells of the tumor, but not the transmission of the tumor (see Rous 1913). Another argument: Because the tumor-causing agent in Rous's chicken sarcoma is not only found in the primary tumor,

Barnard (1925) reported that he was able to image the agent of the roustumor on agar plates by means of an ultraviolet light and with the wavelengths 275 μμ with the aid of a combined illuminator as a rounded or spherical body on the photographic plate. This would suggest a corpuscular nature of the agent. Evidence that the tumor pathogens are particles of considerable and uniform size made it difficult to imagine them as an endogenous agent. According to the results of a series of investigations, it could be assumed that the virus elements obtained from tumor material (in the infectious juice of Rous sarcoma) have the same size and a particle diameter of approximately 60 to 70 mμ (see Elford / Andrewes 1935 and 1936), which changes when

49 Carrel reported (1925: 1083) that the injection of embryo porridge, which he had mixed with tar, indole and arsenic, could cause tumors in chickens, the virus of which can be transmitted further by cell-free filtrates. A. Fischer (1926: 1217; reference from Seiffert 1938: 9, without title) believed that he had generated a filterable, tumor-producing virus by treating tissue cultures with arsenic.

centrifuged speaking speed and presented as granules in colored preparations of the thrown out sediment (see Ledingham and Gye 1935).

To justify the thesis that a living agent is present in the filtrate, it could also be argued that the addition of chloroform significantly impaired or completely canceled out the virulence of the virus, so that it no longer has a tumorigenic effect. Or it could be referred to experiments, according to which the agent was still detectable even in extreme dilution of the starting material. A chemical substance should have been exhausted gradually.

With regard to the tumor virus, too, it can be stated that controversies to understand its nature could not be solved experimentally. The doubts about filterability did not subside, partly because individual authors attempted a cell-free transmission of such tumors such as chicken sarcoma to negative results, partly because positive results could be distrusted with reference to conceivable sources of error. The same can also be said with regard to the counterparty.

Die Dekonstruction of bacteriological Paradigmas of the previous Virus research in Eresult of the Vexperience development

The filterable, invisible agents did not immediately prompt the development of a new theory to understand them. At first the effort was predominant to adapt the new appearance to the traditional explanatory pattern of bacteriology. In the 1930s, most virus researchers were not inclined to give viruses a biological peculiarity. They seemed to be able to make a continuous, seamless transition to virus research and vice versa from bacteriological studies. Virus research was practiced as "bacteriology without a microscope" or the dividing line between the two areas seemed to arise only from the physical limits of the microscope.50 In the filterable agents one usually saw something like "minimal bacteria",

50 "There is no obvious dividing line between Bacteriology and the study of viruses; in fact, it appears to me that the study of the one leads continuously and without break to the study of the other. The only demonstrable dividing-line, if such there be, seems to be one originally imposed by the available methods of study - arbitra- rily imposed indeed by the physical limits of the micro-scope itself. When disease agents were discovered which were too small to be seen and resolved by the best microscopes then existing, morphology could offer no guidance as to the nature of these very small agents. They were thought to be something quite different from ordinary bacteria. There is, I think, no doubt now that had the microscope been more highly developed in those days, much so-called virus work would have been but a natural development of bacteriology.

easily treated like ordinary bacteria. But it was believed that the difficulties could eventually be overcome. It was foreseeable that one day the virus would be made visible with improved microscopes or staining methods and could be separated from liquids with finer filters. In addition, observations could be made that, in certain viral diseases, there appeared to be similarities between filterable agents and the smallest bacteria. The small bodies of various viruses - the vaccine, the mouse and the canary virus - showed, according to Burnet and Andrewes, with reference to photographs (1933: 166), a structure and possibly even a mode of reproduction, “which is essentially similar to that found in ordinary bacteria - is.

There was also a belief that the filterable agents would eventually grow on inactive culture media. And researchers have repeatedly come up with the claim that they have cultivated virus on cell-free nutrient media (see Eagles and McClean 1931, who wanted the vaccine virus to be bred in such media; see also Eagles 1935). However, reports of this type could not be confirmed by other virus researchers (lengthy attempts to test the breeding of the vaccine virus on artificial nutrient media were carried out by Haagen in 1933 and by Rivers and Ward in 1933, among others). The fact that success in this regard had not yet occurred was interpreted as meaning that one had not yet come across suitable soils or that knowledge of the physiology and metabolism of the cell was not yet sufficient. to artificially create those milieu conditions that are necessary for the growth and multiplication of viruses (see Burnet / Andrewes 1933: 162). The search for suitable soils continued unabated until the early 1930s.51 The emerging thesis that the virus could only be propagated in the presence of living cells outside the animal or plant body was the assumption of an “obligatory intracellular parasitism” of the essential virus trait, whereas filterability and invisibility should no longer count as decisive characteristics - prompted an immediate contradiction (see Gildemeister 1939a: 9). Few suspected a condition of virus replication in the presence of cells. At that time, non-cultivability was a thoroughly contestable criterion for differentiating the class of filterable viruses from other “microbes”, as long as it could not be decided whether it was due to essential characteristics of the virus metabolism or only due to unsuitable breeding technology. The assumption that this was only a temporary problem was supported by the fact that it was possible to refer to certain bacteria that only then turned to artificial nutrient media.

51 "In the literature of twenty years ago it is not uncommon to encounter reports in which it was claimed that viruses had been successfully cultivated on lifeless media. These reports have not been confirmed and are presented such claims are rarely made, ”says Rivers (1932: 429).

more if a certain substrate was added to the nutrient substance as a growth factor (for example hemoglobin). 52 Analogous to the fact that there were bacteria that needed special media to grow, in the case of the virus the only issue seemed to be the right one To discover substrate that allowed an in vitro culture of the agent. There was no reason to believe that a bacterium's ability to reproduce in artificial media could depend on its size, so why should the failure to breed the virus, which is known as ultramicrobes, be more profound than reasons only technical shortcomings are responsible (see M'Fadyan 1908: 240 f.), especially since there were also filterable agents for which this already seemed to be successful, agents, which at that time were still assigned to the viruses (see Ruska 1950b: 6). This is how the causative agent of cattle pleuropneumonia, calculated by Roux, Nocard et al. had been described in the form of tiny, fringed and moving spots of extreme thinness to the few types of virus that could be grown on lifeless nutrient media (see Roux / Nocard et al. 1898: 244; Haagen 1939: 176; Barnard 1939 : 8), as well as the causative agent of agalactia.53 They made it possible that, with further knowledge of the physiology and metabolism of the cell, that is, with a more intimate familiarity with the physico-chemical processes within the living cell, the milieu conditions could be artificially created, which are necessary for the growth and multiplication of viruses. This is how the causative agent of cattle pleuropneumonia, calculated by Roux, Nocard et al. had been described in the form of tiny, fringed and moving spots of extreme thinness to the few types of virus that could be grown on lifeless nutrient media (see Roux / Nocard et al. 1898: 244; Haagen 1939: 176; Barnard 1939 : 8), as well as the causative agent of agalactia.53 They made it possible that, with further knowledge of the physiology and metabolism of the cell, that is, with a more intimate familiarity with the physicochemical processes within the living cell, the milieu conditions could be artificially created, which are necessary for the growth and multiplication of viruses. This is how the causative agent of cattle pleuropneumonia, calculated by Roux, Nocard et al. had been described in the form of tiny, fringed and moving spots of extreme thinness to the few types of virus that could be grown on lifeless nutrient media (see Roux / Nocard et al. 1898: 244; Haagen 1939: 176; Barnard 1939 : 8), as well as the causative agent of agalactia.53 They made it possible that, with further knowledge of the physiology and metabolism of the cell, that is, with a more intimate familiarity with the physico-chemical processes within the living cell, the milieu conditions could be artificially created, which are necessary for the growth and multiplication of viruses.

With the perfection of filtration technology (especially with graduated membrane filters), the infectious agent was finally separated from liquids. Filter types with standardized pore sizes were developed, so that the size of different virus types - depending on whether the pores were passed or not - could be measured comparably.54 But with these improvements it

became apparent that the filterability of a pathogen was largely is dependent on the filter type and filtration conditions (e.g. pressure, duration), not only on the size and surface of the virus. Collodion membranes, too, could not simply be seen as sieves, which would hold back particles whose diameter is larger than their pore size.

52 According to Fildes, a substance or a chemical group that participates in the synthetic chains necessary for bacterial growth as an essential factor but cannot be synthesized by the bacterial cell itself - according to factors of this type as "essential metabolites" - wins, the meaning of a
"Growth substance" that has to be added to the nutrient medium if propagation is to be made possible (1940). In addition to growth-promoting substances, attention was also paid to growth-inhibiting substances (see also Doerr 1944b).

53 Frequent disease of the mother sows due to infections of the suckling at birth.

54 The average pore size of a given membrane was determined by the rate at which a given amount of water flowed through a membrane area of known size under standard conditions, taking into account the water content of the membrane (see Burnet / Andrewes 1933: 165).

Stiffness is dependent (1908: 166). A few years later, at a meeting of microbiologists in Dresden, Doerr had taken a critical stance on the problems of virus filtration and was concerned with the nature of the medium (the nature of the liquid used for the suspension), the forces of molecular attraction, and capillarity, Filtration duration and pressure received (1911). With the further refinement of the filtration techniques, the process dependency of the facts gained became more and more obvious. "The difficulties become insurmountable if the vaccination success with the filtrates turns out to be very uncertain and fluctuating, as with the flu ... All filters ... physically follow the Poiseuille law of filtration through capillaries, the average width of which is determined thereby .. .
"Bottlenecks" ... The requirement of "isoporosity" practically remains mostly a pious wish "(Schmidt 1935: 1661). In addition, difficulties arose in distinguishing viruses from other agents according to their filterability, because one had come across some pathogens that could pass through ultra filters, but had to be counted among the bacteria (such as, for example, Pfeiffer's influenza bacillus)), while at the same time it turned out with some ("larger") viruses that these filters were impermeable to them. These difficulties could not be eliminated by the construction of new filters (membrane filters made of collodion and other material) and the approximate determination of their “effective pore size”.

And just as the property of filterability as a criterion of value for the assessment of the viral nature lost to the extent that difficulties arose with the improvement in technology to separate the empirical results from the type of observation conditions, so did the property the invisibility with the perfection of techniques as not reliable for the identification of infectious agents as viruses, as will be explained below.

Originally, it was widely assumed that the biological uniformity of the viruses could be derived from their dimensional association. Even in texts from the late 1930s, one occasionally comes across sentences that express a connection between the size differences of the agents and their biological characteristics. For example, in an article published in 1937, Haagen claimed: “The dimensional limitation goes up At the same time, the virus is biologically separated from the other microorganisms, insofar as the rickettsia already differ significantly from the former in their cultural claims ”(1937: 465) .55 However, some (“ small ”) bacteria had already been encountered that could hardly be made visible

In certain diseases in which filterable viruses appeared to be involved, the microscope revealed the existence of so-called "inclusion bodies". In 1904, Borrel reported the occurrence of the smallest copuscular elements in sheeppox and chickenpox, which he regarded as the causative agent of these diseases. Similar observation results were reported by Paschen (1906), who had examined human pox material, which led to the assumption that at least some viruses could be visualized using ordinary microscopic technology. This discovery was followed by a lively search for morphological elements. Such findings were found, for example, in a viral disease of the canaries (see Burnet 1933), in Molluscum contagiosum56 (Goodpasture / Woodruff 1931), in Psittacosis (Levinthal 1930) and Ectromelia, a viral disease of the mouse (Barnard / Elford 1931: 530). Von Prowazek (1911) introduced the term “elementary body”, which is still used today, to name such elements. Lipschütz pleaded in 1930 to call them "Chlamydozoa" and "Strongyloplasmas". However, this proposal did not prevail. The “elementary bodies” gave rise to a debate lasting several years, in which it was disputed whether these bodies were identical to the real pathogens. Some researchers suspected that the various cell inclusions were nothing more than special morphological virus forms, which corresponded to their intracellular need for reproduction. The virus particles attacked the cell, injured it, and as a result, inclusions would be formed from the cell material. Other researchers saw only a cellular reactant in it. The particles would penetrate the cell, which reacted with the formation of a plastic material that would merge around the virus and partially or completely encase it. Later, as a result of modern color differentiation and tissue engineering, the view spread that virus and cell changes (inclusion bodies) should be strictly separated from one another (see Haagen 1937: 468).

The visibility of virus species was further improved through the further development of optical devices, the use of ultraviolet light57 and special staining processes. In the 20s and 30s, new technologies such as dark field lighting and UV microscopy became accessible. Virus particles could be made visible indirectly by working in the dark field of the microscope, that is, by using the indirect lighting option to reflect the light rays hitting the side. It could light a lot more

55 Rickettsia were initially classified as bacteria. However, because they passed filters and only developed intracellularly, they were later viewed as a virus type with specific characteristics (for the history of the classification of Rickettsia see Weindling 1995: 81 f.). This assignment no longer applies today because rickettsiae differ from viruses in their DNA / RNA content and their cell wall containing muramic acid. They are determined as a group of obligate cell parasites that cannot be cultivated outside of living cells and belong to the class of gram-negative eubacteria (see Scherf 1997: 405).

56 Contagious skin polyp.

57 For early attempts to use ultraviolet light, see Köhler 1904.

particles in a weaker refractive matrix. In this way, objects could be perceived as bright points or spots of light. The use of UV microphotography also made smaller particles more visible than was possible with normal light microscopic techniques because the resolution of a microscope depends on the wavelength of the light.58 However, with these means the size of the particles could only be can be opened up indirectly. As a result of the increased resolving power, contamination in the cultures had a much more disturbing effect than when taking pictures in ordinary light. No other morphological control could be carried out because of the "ultravisibility" of the agent, so that it could not be determined with certainty whether the sight was the pathogen or a contamination.

"The greatly increased resolving power," so Pfeiler and Simons (ibid.), "May it be that the morphologist may wish that the aetiological research of filterable virus types can be fatal under certain circumstances ... It is the case today bacteriological culture technology is completely impossible to produce pure cultures which, apart from the pathogen in their medium, contain no other particles standing at the colloid boundary, let alone 'optically empty'; on the contrary, such cultures inevitably contain more or less large dust and nutrient medium particles, possibly also other living filterable microorganisms. " It could also not be excluded that the microorganisms change morphologically due to the chemical effects of the ultraviolet rays.

In the early 1930s, with the help of these techniques, when examining Rous sarcoma cells, Zweibaum had seen something quite different from what Barnard wanted to see in 1925 (see above), namely abundant quantities of filaments in which the smallest, round granules were stored and which could be stained and blackened during osmosis.59 He perceived the filaments as certain cell organelles (cell structures that perform certain functions in the cell), namely as mitochondria (mostly rod-shaped organ

58 In order to obtain clear images of virus particles, a light source was used, the wavelength of which comes from the ultraviolet part of the spectrum and which is not too large in relation to the order of magnitude of the particle to be measured. "In addition to a monochromatic ultraviolet light source, of course you need a quartz lens and quartz prism system and a device that allows you to find the objects you are looking for in visible light. After the object has been set with visible light, it is brought into the focal point of the ultraviolet rays selected for recording by means of calculated fine adjustment, and then the image invisible to the human eye is photographed with ultraviolet light dark field illumination "(Burnet / Andrewes 1933: 164).

59 Osmium is a precious metal belonging to the group of platinum metals, and "osmic acid" is a compound that is used in microscopy to stain and harden biological preparations.

len, which occur in all eukaryotic cells, multiply by division and have their own genetic material and carry out the material conversions and shape-forming processes) .60 As he reported, the cell organelles would look very much when viewed in the dark field due to the influence of light soon disintegrated into individual, smallest, luminous granules and after this decay could not be distinguished from the Rous agent bodies at all optically, which would suggest that the filiform elements and said bodies are very close with regard to their chemical structure and probably also in genetic relation may be related or identical (Zweibaum, 1933: 359). Some of his pictures give the impression that as if the filiform mitochondria emerged from these small granules by stringing the latter together. According to Zweibaum, the mitochondria of the Rous sarcoma cells should differ from those of the homologous normal cells, which can be seen in their staining behavior (behavior towards vital dyes) and their rapid disintegration into small granules under the influence of light when observing the dark field. Amies also found tiny bodies in the fraction from normal chicken tissue (leukocytes, spleen tissue) obtained in the same way as the Rous agent (high-speed centrifugation), which was not distinguishable from the Rous agent bodies neither in the dark field nor with regard to their color behavior - ren (Amies, loc. cit., p.141; see also Graffi, loc. cit., 520). According to Zweibaum, the mitochondria of the Rous sarcoma cells should differ from those of the homologous normal cells, which is evident in their staining behavior (behavior towards vital dyes) and their rapid disintegration into small granules under the influence of light when observing the dark field. Amies also found tiny bodies in the fraction from normal chicken tissue (leukocytes, spleen tissue) obtained in the same way as the Rous agent (high-speed centrifugation), which was not distinguishable from the Rous agent bodies neither in the dark field nor with regard to their color behavior - ren (Amies, loc. cit., p.141; see also Graffi, loc. cit., 520). According to Zweibaum, the mitochondria of the Rous sarcoma cells should differ from those of the homologous normal cells, which can be seen in their staining behavior (behavior towards vital dyes) and their rapid disintegration into small granules under the influence of light when observing the dark field. Amies also found tiny bodies in the fraction from normal chicken tissue (leukocytes, spleen tissue) obtained in the same way as the Rous agent (high-speed centrifugation), which was not distinguishable from the Rous agent bodies neither in the dark field nor with regard to their color behavior - ren (Amies, loc. cit., p.141; see also Graffi, loc. cit., 520). what is evident in their coloring behavior (behavior towards vital dyes) and their rapid disintegration into small individual granules under the influence of light when observing darkfields. Amies also found tiny bodies in the fraction from normal chicken tissue (leukocytes, spleen tissue) obtained in the same way as the Rous agent (high-speed centrifugation), which was not distinguishable from the Rous agent bodies neither in the dark field nor with regard to their color behavior - ren (Amies, loc. cit., p.141; see also Graffi, loc. cit., 520). what is evident in their coloring behavior (behavior towards vital dyes) and their rapid disintegration into small individual granules under the influence of light when observing darkfields. Amies also found tiny bodies in the fraction from normal chicken tissue

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The diffraction patterns created with dark field illumination did not make it possible to directly determine the size of the particles that caused them. To determine the actual size of the virus particles, the observation in the colored preparation was also unable to provide exact values. It was known that in a Giemsa-stained smear, for example, the infectious agents appear to have a much larger diameter than in the unstained preparation. The surrounding color envelope only brings the pathogens into the visibility range of the light microscope. So it could only be concluded from a colored preparation that the size of the particles is smaller than that specified by the colored preparation.

The fact that viruses were immediately visible in 1939 with the help of electron microscopy (Kausche, Pfankuch, Ruska 1939) 61, in which very fast electron beams take the place of light rays, did not at all hear the difficulties in determining nature of the virus. Damage was already observed in the first attempts to image biological objects using an electron microscope. And there were sales

60 This means that they have genetic continuity, that is, they only multiply through self-division and have autocatalytic growth capacity. It is believed that in the course of evolution they have arisen from bacteria that have migrated into the cell.

61 Bacteria and viruses were among the first objects in electron microscopy. Because the penetrability of the electrons is extremely low, the usefulness of the electron microscope was first demonstrated on such small and thin biological objects (see Hoppe 1991: 330).

changes to the objects described. This had sparked a great deal of skepticism about the results from the “super microscope” among many biologists. And so Ruska et al. There are also reasons to take precautionary action when presenting your “super-microscopic” images that “our newly found structures would be artifacts that were created by vacuum or electron beams. Such an objection is particularly obvious if previously unknown envelopes or capsules appear on the bacteria ”(von Borries / Ruska / Ruska 1938: 923 f.). The following difficulties arose for the examination of biological objects with radiation: “1. The preparation must be in a high vacuum; this precludes the investigation of life processes from the outset. 2nd The specimen is heated slightly too high during strong radiation and destroyed by the rays. 3. After passing through the object, the electrons suffered speed losses of different magnitudes, depending on the layer thickness or specimen density irradiated. Electron beams of different speeds behave similarly to light beams of different colors in optics. They are deflected to different degrees by the lens, so that the chromatic error of the lens prevents a good image ”(Rüchardt 1938: 1836). Electron beams of different speeds behave similarly to light beams of different colors in optics. They are deflected to different degrees by the lens, so that the chromatic error of the lens prevents a good image ”(Rüchardt 1938: 1836). Electron beams of different speeds behave similarly to light beams of different colors in optics. They are deflected to different extents by the lens, so that the chromatic error of the lens prevents good imaging ”(Rüchardt 1938: 1836).

The use of electron microscopy seemed to cloud rather than sharpen the picture of the viral nature. The results obtained with the new method, as Ruska explains in 1950, made it necessary to understand “that the virus types do not show any biological connection. They turned out to be partly macromolecular infectious substances, partly as the smallest organisms, partly as structures for which only the indefinite term virus is initially available. "" Virus "is therefore not a concept of biological systematics, but a" collective name " for various agents. Until the advent of electron microscopy, forms of the smallest microbes would have been classified under the collective term "virus". But 10 years after the start of electron microscopic work, all criteria

The introduction of tissue culture technology was particularly important, which did not mean that the intracellular location of virus replication, which could be taken into account with this technology, was unknown. This method was initially used only to preserve the virus in the tissues, and at first it only allowed the virus in a few at best

62 However, according to Ruska in another publication, although "virus" is not a concept of biological systematics, "there is still a need for an order of diverse manifestations." The summary of all filterable virus types in a single order "Virales" and their others Subdivision into subordinates, families, genera and species is "unbiological" in the current form. But they satisfy the practical need for a general way of communication (Ruska 1950b: 57).

To continue cultural passages in an infection-proof form. The further development of the method then finally enabled the permanent cultivation of virus, which was first achieved by researchers who were completely familiar with cell research, according to Carrel (1925), who had proven that the Rousian chicken sarcoma virus was found quantitatively in tissue explants increased and continued in cultural passages. But the improvement of breeding techniques also caused problems. Differentiating viruses from bacteria according to whether artificial cultivation is successful or not turned out to be not reliable enough because there were some bacteria that required special nutrient media to grow, whereas some filterable pathogens such as mycoplasma could be grown without direct contact with living cells. It was also found that some types of virus lost pathogenicity in long-term breeding and that tissues suppressed some viral traits. In general, it was still largely unclear what role tissue plays in viral propagation. It was therefore known that a classification according to the affinity of the pathogens for the various tissues of the organism and the clinical manifestations that cause them could only be a makeshift one (see Seiffert 1938: 15). It was also one of the first attempts to systematize the types of virus, led by the experience that the settlement of the types of virus in the organism seemed to obey a tissue specificity (Herzberg 1939: 17). The fact that virus replication was only possible in the explant was confirmed by the insight gained before virus breeding that there must be very close relationships between the host and the virus. However, it remained unclear whether intra- or extracellular virus replication takes place. Two mutually exclusive interpretations were still possible, either that the virus feeds on the cell in the manner of an animated pathogen and multiplies autonomously, or that the virus is an enzyme-like substance whose regeneration is only possible by the living cell (see Hallauer 1938: 368). The uncertainty continued for several years in virus research. In a work published in 1950, Bedson took the previously widespread position that the various types of virus were not of a uniform nature. "Where is one to draw the line which is to separate the microbial midgets from the unorganized, nonliving, autocatalytic infective agents? It is impossible to say be-cause, from the very small-read up to the largest virus, there is an unbroken series, not only of particle size, but also of complexity of structure; on merges into the next with no clear indication of a gap suggesting division of the group ”(1950: 18-19).

In 1938 Doerr attributed what he believed to be unjustifiable adherence to the understanding of the virus as a biologically homogeneous entity to the fact that methods had to be used “which have little contact with the research resources of microbiology; This must ultimately have an impact on the notion that the special and uniform methodology also has a special and uniform object (i.e. biologically

ce or related objects of a special kind - KL) ”, a conclusion that is all the less permissible, since the methods used are almost always those that are to be characterized negatively, such as the absence (light -) microscopic examination and the exclusion of larger dimensions by filtration (Doerr 1938: 98; 13). And a few years later: The object of virus research is only the means necessary for its scientific penetration, "in terms of methodology and technology", although it is understandable to a certain extent,

“If the constant use of identical research resources ultimately results in the idea of a research object that is not only technically homogeneous, but ... especially in biological terms, an idea which, once it has taken root, is to be justified afterwards , as well as this wants to go ”(Doerr 1944a: 7). In this essay, Doerr criticizes the fact that either conclusions can be drawn from what is supposed to be an inherent whole, based on considerations that apply to individual types of virus, or that one looks for more or less hypothetical features that could be attributed to all types of virus and that serve as starting points for Considerations about the nature of the same seem appropriate. In any case, one would deviate from the facts for the purpose of generalizing statements (ibid., 7 f.

It follows from the fact that the groupings of virus types as they were formed were ultimately anchored in the research funds used, that the classification could not have been unaffected by changes in methods and procedures. The methodological-technical uniformity of the object of virus research, which was highlighted by Doerr in 1944, was dissolved with the further development or application of new techniques. With changes in the conditions of fact production, specialization, improvement, change and the introduction of new experimental conditions or procedures, these could no longer act as conditions of coherence as before - as conditions for establishing similarity relationships between the investigated agents. 63 In the 1930s, therefore, an increasing number of judgments regarding the state of virus research emerged, according to which, with the development of these and other methods, the general understanding of the virus nature was further removed instead of being approached. In 1932, Rivers suggested that the "virus" was only a collective term for the whole

63 According to Buchwald, the robustness of a taxonomy is enhanced if it is not only thanks to the use of a special instrument, but is in line with many other instruments with which the classification issue is pursued, but in different ways (1992: 44). As our case study shows, the opposite can happen at first. While viruses could initially be described as filterable agents that were invisible by light microscopy and could not be grown on cell-free culture media, the coherence of the above-mentioned characteristics was softened further. For example, there were submicroscopic pathogens that could not be filtered, agents visible by light microscopy that could not be cultivated on cell-free culture media, and the like. It took a long time to develop

There were various things, a term that would include both “micro-microbes” and very small inanimate agents. “The dividing lines (according to which viruses could be separated from bacteria, protozoa, etc. - KL) are now even more blurred than was the case at the turn of the century,” says Doerr in 1938 (1938: 25 f.). And Seiffert in the same year: "Virus is not a scientifically based biological term, as is sometimes believed, but only a method-related collective name" (1938: 1). Kausche 1939: “At the current level of our knowledge, the refinement of the research methods seems to dissolve this collective term 'virus' in such a way that it is now necessary to distinguish between species that a living being with the properties of reproductive ability, are similar to breathing and their own metabolism, and those that appear to lack this characteristic and, due to their mode of action and conditions of action, are to be classified as active substances of chemically inanimate nature ”(1939: 9f.). And Blumenberg (1943: 629): “The name of the virus is only given the lack of unity by name, the question of the nature of a virus must be asked and answered anew in each individual case.” The concept became valid put to the test because the individual types of filterable viruses differed greatly in their chemical nature, which could be highlighted thanks to improved methods (for example, perfecting the centrifuges would make it easier to separate the viruses from accompanying substances and thus chemical analyzes) make available). It was found that many plant viruses could be characterized as relatively simple nucleoprotein molecules, whereas animal viruses appeared to have a complex structure, that is, a molecular concept to understand how the results of chemical and physicochemical studies could be derived (see Smadel / Hoagland 1942: 96). Nonetheless, the thesis that plant and animal viruses differ from each other in the implied way did not only meet with approval. According to Pirie, it could also be due to the methods used at the time that it was not possible to identify, for example, the characteristics of the flu virus in leaf extracts from diseased plants. whereas animal viruses appeared to have a complex structure, that is, a molecular concept to understand them, as the results of chemical and physicochemical investigations (see Smadel / Hoagland 1942: 96). Nonetheless, the thesis that plant and animal viruses differ from each other in the implied way did not only meet with approval. According to Pirie, it could also be due to the methods used at the time that it was not possible to identify, for example, the characteristics of the flu virus in leaf extracts from diseased plants (1946: 575). whereas animal viruses, on the other hand, appeared to have a complex structure, that is, a molecular concept to understand how the results of chemical and physicochemical studies could be derived (see Smadel / Hoagland 1942: 96). Nonetheless, the thesis that plant and animal viruses differ from each other in the implied way did not only meet with approval. According to Pirie, it could also be due to the methods used at the time that it was not possible to identify, for example, the characteristics of the flu virus in leaf extracts from diseased plants. that plant and animal viruses differ from each other in the indicated way, not only on approval. According to Pirie, it could also be due to the methods used at the time that it was not possible to identify, for example, the characteristics of the flu virus in leaf extracts from

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Attempts to focus virus phenomenology on other invariant features in order to develop a more stable classification that approximates the “natural order” failed again and again. The “similarity relationships” that were obtained fell apart again and again with further empirical advances: the tests were carried out, among other things, to determine whether the analysis of immunity relationships, immunity to virus infections, antigen functions (whether viruses have a specific antigen structure that gives rise to specific antibodies) and the serological responses of the virus species can be invariant characteristics that differ significantly from the conditions that were observed with other transferable agents. In 1928 Schultz had assumed that no type of virus was capable

be to form "complement-binding" antibodies or "precipitins", and that the so-called "Virolicid" immune substances were the only type of antibody that was also characteristic of the virus species (1928; cited from Doerr 1938: 90 f.). However, it was determined that the immunizing power of the course of the infection is not dependent on the agent being one of the virus types. The efforts to gain general aspects of biological nature from the study of immunity conditions were assessed by Doerr (1938: 86) as unsuccessful in that it was not possible to determine fundamental differences between virus types and other infectious agents. The antigen functions of the virus types did not reveal any fundamental deviations from the antigen functions of other infection substances or microbes.

It was also checked whether viruses can be differentiated from other pathogens based on the preferred hosts. But no fundamental differences could be determined in this regard either. It was not possible to classify viruses according to host affinity. Some viruses could be propagated in multiple hosts, leading to the difficulty that different names were often used for the same virus (see Ruska 1950b: 16), others could also lose the ability to infect a particular host. It was also possible to infect one and the same plant or animal host with numerous types of virus, which differed greatly in other respects in terms of dimensions, morphology, chemistry and serology (see Fraenkel-Conrat 1974: 11).

Another attempt was to identify viruses as a separate category of infectious entities. In 1928 Rivers took the view that the virus caused pathogenic effects in its host which, although not completely different from other diseases, "yet sufficiently different from them in regard to phenomena related to proliferation and degeneration to warrant placing such agents in a group by themselves ". Based on the changes assumed to be consistent, he came to the conclusion that an "intimate type of parasitism exists" (1928: 111) in viral diseases. Bedson later argued that what was common to the virus types could not be found at the level of virus-related diseases: "... there is no fundamental difference in the clinical and epidemiological be-havior of the diseases caused by these viruses which might lead one to think that some viruses were of an essentially different nature from others "(Bedson 1950: 19). Andrewes rejected symptomatological classifications with the argument that viral properties such as virulence, mobility and persistence are largely unsuitable for justifying a classification because of their variability (Andrewes 1950: 165; cited in van Helvoort 1994a: 216). Ruska emphasized that what you get in this way is not a "systematic group". "The same or different disease symptoms caused by different types of virus can Andrewes rejected symptomatological classifications with the argument that viral properties such as virulence, mobility and persistence are largely unsuitable for justifying a classification because of their variability (Andrewes 1950: 165; cited in van Helvoort 1994a: 216). Ruska emphasized that what you get in this way is not a "systematic group". "The same or different disease symptoms caused by different types of virus can Andrewes rejected symptomatological classifications with the argument that viral properties such as virulence, mobility and persistence are largely

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in our opinion, neither serve to summarize larger virus groups, nor to separate individual species in widely separated groups. Only where there are morphologically identical virus forms can the unequal clinical pictures that they cause serve to separate related virus types ”(1950a: 389). The symptomatology had previously been discussed as having an essential role in explaining the nature of the virus, because according to the latter it was only a matter of looking for common characteristics of how the infected organisms react to the viruses (see Gsell 1967). .

Z.U AGREE VREQUIREMENTS, UNDER WHICH IT IS ONE WLIZARD FROM BACTERIOLOGICAL TO MOLECULAR GENETIC VI understand

The history of virus research in the 20th century is usually described as a continuous process, as a story of the progressive unveiling of virus nature (see Waterson 1978: xii; Hughes 1977: 75 ff .; for a critique of this concept see van Helvoort 1994a: 187). Our analysis of the case study material, however, has shown some things that lead away from such a historical picture. In particular, it has been shown that refinement and expansion of the technical means and procedures, which are generally seen as the guarantee of incessant progress in the knowledge of nature, rather led to setbacks in the period under consideration (for example in the development of the virus classification) and the gap between the conflicting parties in virus research. Something had been discovered with the “filterable” virus, which according to the traditional concepts, which had mostly proven their worth in the research of infectious diseases, could not be visualized by all researchers. There were many different interpretations of the nature of this phenomenon, which were brought up against each other in the field. Neither side could provide any experimental evidence for this or that concept, which all researchers should have recognized. This means that the decision as to whether this or that explanation best expresses the “true” nature of the virus could not be “objectified” empirically. Every version to interpret the phenomenon remained vulnerable, Facts presented to the specialist public could often be reinterpreted as fictions by opponents, in that they depicted the dependency of the findings on the observation conditions, the local situation of the experiments, the research-related nature of the attribution of characteristics and the like. Like. brought into play as sources of error. At the time, findings from certain virus researchers were often not confirmed by other researchers as a result of their own experiments, or the observations could not be reproduced by all scientists involved with the virus. Contrary findings were often communicated, or the findings that had been checked were considered artifacts. the research-related nature of the attribute attribution u. Like. brought into play as sources of error. At the time, findings from certain virus researchers were often not confirmed by other researchers as a result of their own experiments, or the observations could not be reproduced by all scientists involved with the virus. Contrary findings were often

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tet. As for the justification, reasons of various kinds could also be used to reject the debated positions. Findings that were used to empirically confirm a suspected relationship were often soon joined by negative findings shared by other researchers. As carefully and deliberately as the techniques had been used in the trials, and regardless of the fact that each party could offer credible reasons to represent their position and come up with empirical evidence - which is explained by the fact that “the various opponents, construed 'widely diver- ging research objects which they identified as the, virus' ”(van Helvoort 1994a: 202) - at no time did they offer compelling reasons that would have led the other party to

To defend the concept that viruses are endogenous, findings were often made with the claim that organisms that were protected against exogenous infections and were therefore free of viruses in all parts, mostly after a few weeks could detect plenty of virus. Against the concept of endogenous virus formation, it could be argued that exogenous infections cannot be completely ruled out due to technical deficiencies in the experiments carried out and that laboratory infections should be expected (see Seiffert 1938: 9). There were sufficient reasons to suspect that the virus had been present in the cultures from the beginning, but in such low concentrations that it had not been identified (see Smith 1936).

The failure in the attempts to prove respiratory processes in viruses was only attributed to researchers who considered the virus to be a living being due to the experimental shortcomings still existing or to the fact that under the given artificial

64 Scientific facts that Knorr-Cetina (1984, 1985a, 1985b), Collins / Pinch (1982), among other things, resulted from processes of social construction can be "deconstructed" again. The transformation of fictions into facts or from controversial discussion points into indisputable facts relates Latour to a process of “modalization”. By adding modalities to factual claims, they gain the character of personal opinions or speculations or ideas that are tied to local or temporal peculiarities of opinion formation. A sentence loses its factual character if the readers go back to where the sentence originated, to the mouths and hands of those who put it up (Latour, 1987: 25). Latour speaks of a sentence added “negative modalities”, when an assertion is traced back to the production conditions. On the other hand, he calls those sentences “positive modalities” that lead an assertion away from its production conditions, whereby the assertion gains the status of a fact (ibid., 23; see also Latour / Woolgar 1980: 79 ff.).
"Scientists in current controversies construct and employ histories of medicine, technology, and science to support their arguments or to deconstruct opponent's arguments ... This is more than a debating strategy. Constructing history is one means by which scientists (re) construct rules for verifying facts and findings; that is, constructing history is part of the verification process in science ”(Fujimura 1996: 53).

conditions the virus may have been damaged (see Seiffert 1938: 7). Opponents, on the other hand, saw the failure as something that spoke against the living nature of the agent.

The claim that after a few passages numerous phages were obtained from phage-free cultures (dysentery, typhoid, coli, etc.), which should be evidence that the bacterial-dissolving appearance arises from bacteria alone (that the resolution by a bacterial self-produced autolysin), it could always be countered that many cultures contained bacteriophages from the outset, which were often difficult to detect. The complete bacterial dissolution claimed by d'Herelle was also not unanimously confirmed. It was Gildemeister, for example, who - as stated above - counted the phenomenon discovered by d'Herelle to the variability phenomena of the bacteria, neither by microscopic observation nor by application of histological technology,

Again and again the criteria for the dispute were set, by which the reliability of the exclusion of cell residues from tumor filtrates was measured, the reliability of such procedures as the filtration, pulverization or the use (cell-dissolving) glycerol in the treatment of tumor material before its vaccination to healthy animals. Researchers who saw the origin of the virus in the cell could argue that even if cancer nests or spots that were microscopically suspect to be found in the filtrate could not be found in the filtrate, it cannot be ruled out that there are still individual cancer cells in the circulation and had changed their character within the possible limits. Or you could refer to experiences that significant amounts of cancer cells must be injected in the form of tumor porridge in order to cause tumor formation. There were always occasions to attack or defend allegations that tumor transmission was initiated by cell-free filtrates and that the viral nature of cancer had been shown.

Statements about the fact that viral elements obtained from infectious juice from Rous sarcoma by centrifugation are of equal size to one another and show up as granules in colored preparations of the ejected sediment were raised, among other things, with the argument that the fact that all particles are the same size or approximately the same size as one another, a natural consequence of the technique of fractional centrifugation. The reason given that the assumed morphological homogeneity of the virus elements was generated by the centrifugation experiments was, for example, based on the following arguments: You can spin out normal tissue extracts (15,000 revolutions

65 He later expressed in a lecture that he had to be convinced of the complete bacterial dissolution (1923: 184 f.).

per minute) of tiny bodies of the same size, which in every respect resemble the elementary bodies that can be obtained from an active cell-free tumor juice (Rous sarcoma) with the same technique. These carriers of the specific virus effect did not differ in any way from other contaminating particles of the same size (see Fraenkel / Mawson 1937).

These examples may suffice to illustrate that the riddles that the nature of the virus posed to researchers during the period under review could not be progressively unraveled according to empirical success (in bacteriology, plant pathology, etc.). The improvement in research conditions, the accumulation of empirical data, the growing number of virus discoveries - at the end of the 1930s well over 100 diseases caused by filterable but not detectable pathogens (Heilmann 1940: 65) were more likely to lead to uncertainty of what you thought you already knew about viral nature. With the development of the methods used, it seemed less and less possible to say how viruses should be understood in a very general sense, whether it was animal or plant, "big" or "small" viruses. The empirical success did not alleviate controversies about the understanding of viruses, did not gradually reduce them, but sparked them again and again.66

It must now be asked how modern (molecular-genetic) understanding of virus nature has come about if it cannot have resulted from the empirical progress of virus research alone. The author of these lines is not yet in a position to provide an exhaustive answer to this question, which has been tested on the history of scientific material. This requires further elaborate studies. But there is still so much that can be said that a process in which virus researchers made use of terms from other disciplines (inheritance research, biochemistry and other areas) has contributed to the development of modern understanding of viruses in order to master the interpretation problems and that To consolidate the positions they each represented in the debates. They got the "gene" the “macromolecule” or the “nucleic acid” in the argument. This also made the virus phenomenon interesting for geneticists, chemists, etc., and the dispute about its true nature reached beyond the circle of virus researchers.67 This was the start of a development.

66 In understanding the new sociology of science, consensus arises from a construction process. "Since the settlement of a controversy is the cause of Nature's representation, not its consequence, we can never use this consequence, Nature, to explain how and why a controversy has been settled" (Latour 1987: 258).

67 “Finding out the origin and essence of life was and remains the last and highest goal of science, and the properties of the virus-like infectious substances, especially the minimal and at least minimal dimensions of their units, justify the expectation to come closer to this goal . Only in this way is it understandable that the results achieved by the specialist were able to arouse the interest of the broadest circles so quickly, and that not only biologists, but also chemists and physicists began to deal with the "true nature of the virus species" (Doerr 1944a: 1).

at the end of which one finds the borrowed terms in a theoretically ordered relationship to one another, as expressed in the modern version of the virus term, a relationship which, however, was the result of a longer development process and not its prerequisite, which is itself the researchers would only have become aware of it step by step. Initially, the “virus” was only suspected by individual researchers as something that could be
“Gene”, the “macromolecule” or something similar, whereby it was a question of free discretion whether or not one was guided by similarity relationships constructed only at the conceptual level68.

The motivation to do this arose from the insight born in the seemingly endless debates that a generally accepted understanding of viral nature would hardly emerge from the traditional practice of researching viral infectious diseases. With the help of experimental results and observations structured according to this or that concept, the various parties created their own areas of experience, from which they then found evidence to justify their concept. As each side perfected its approach, the line between the parties was drawn more sharply, the controversy became more radical. But in the process, conditions were also enriched that prompted researchers to look for new reference aspects of research, according to which the virus phenomenon could be observed and evaluated differently than was customary in the conventional activity. With the change of perspective - with the consideration of the virus appearance from the control room of "outsiders" (geneticists, chemists, physicists etc.) - the expectation was linked that the controversies about whether viruses should be counted as living beings or as a soluble one could be ended Substance or an enzyme are to be understood.

The fact that virus researchers consulted terms from this or that discipline to deal with explanatory problems cannot be seen as an inevitable consequence that they should have drawn from the results of their empirical work (otherwise there could be no question of a change of perspective). .69 These were terms that had emerged regardless of the context of virus research. "... our knowledge of viruses," said Darlington in a retrospective at the beginning of the 1950s, "has grown up in the same half century as genetics. But the concepts used have been quite independent until recently ”(1951: 321). For the fact that

68 This is in contrast to the similarity relationships in the early classifications. For example, certain diseases of humans, cows, horses, sheep and pigs have been combined under the term “smallpox” because they are similar in that they are all characterized by rashes. From today's perspective, it appears to be faulty. "Several of these diseases were indeed caused by pox-viruses, but the deficiencies of this symptomatological classification are highlighted by the inclusion of chickenpox and the, great pox '(syphilis) in the same category", as Fenner explains (1988: 3) .

Placement of the virus with the gene as well as with the macromolecule and other terms did not result directly from the empirical experience gained in dealing with the virus, speaks the following:

These are terms that were still very controversial. The answer to the question of whether viruses are "organisms or ... chemical molecules ... is (is) very difficult, since there is no generally accepted view of the definition of these two basic terms in either chemistry or biology", see Schramm (1942b: 791) .70 There was no unanimous opinion on the applicability of the molecular term, which had been derived from the behavior of simple chemical compounds, to highly polymeric organic substances and especially to colloidally soluble proteins. According to Doerr, it was up to the "free discretion" whether one wanted to speak of proteins of giant molecules or of molecular aggregates, "especially since the bonds that hold the units together are no longer known, than that they seem quite loose and can easily be blown up ”(Doerr 1944a: 11). Nor was there a generally binding version of the term for genes, so that in this respect it was left to every researcher to certify or deny the virus a similarity to the gene. "... depending on the a priori or technical attitude (sometimes) the common, sometimes the different moments were brought to the fore ..." (also

69 For the analysis of such a process, which was initiated by the creation of new reference points for research - thanks to the borrowing of foreign disciplinary concepts - and which further led to a new, coherent knowledge, the reception of the Fleck heritage is very helpful. He describes the establishment of relationships between terms from different disciplines, which he examined using the example of syphilis research, as “active couplings”, explaining why these and not other couplings were based on the cultural-historical context who then determined the biographies of the researchers involved. With "active couplings" it is expressed that interdisciplinary links that develop a new discipline or initiate a new scientific specialty, are characterized by uncertainty. Fleck draws attention to such uncertainty with regard to the interdisciplinary history of the emergence of serology. He explains that the modern concept of syphilis was not the only logical option. If the pioneers in this area had relied on connections other than those which they had then realized, it would have been possible to come up with completely different disease classifications, including other disease units, among which syphilis as a disease unit in the demarcations, such as they apply today, could not be found at all (<1935> 1980: 32 f.). Fleck explains the coupling as a "point of intersection of the development lines of some collective ideas ... “Furthermore, they functioned as conditions for the cognitive work, which consisted in determining the“ inevitable results ”that could be determined under the given conditions. In order to make it believable that the reference to terms from other disciplines is one of the prerequisites required to fulfill the research concern and to adequately grasp the research objects, the subsequent assumptions that can be derived from this - the “passive coupling”, how to it can be named after Fleck (ibid., 56) -, empirically substantiated. The requirements “correspond to the active couplings and form the collective part of the recognition. The inevitable results resemble the passive coupling and form what is perceived as objective reality "(ibid.). which consists in determining the “inevitable results” that can be determined under the given conditions. In order to make it believable that the reference to terms from other disciplines is one of the prerequisites required to fulfill the research concern and to adequately grasp the research objects, the subsequent assumptions that can be derived from this - the “passive coupling”, how to it can be named after Fleck (ibid., 56) -, empirically substantiated. The requirements “correspond to the active couplings and form the collective part of the recognition. The inevitable results resemble the passive coupling and form what is perceived as objective reality "(ibid.). which consists in determining the “inevitable results” that can be determined under the given conditions. In order to make it believable that the reference to terms from other disciplines is one of the prerequisites required to fulfill the research concern and to adequately grasp the research objects, the subsequent assumptions that can be derived from this - the “passive coupling”, how to it can be named after Fleck (ibid., 56) -, empirically substantiated. The requirements “correspond to the active couplings and form the collective part of the recognition. The inevitable results resemble the passive coupling and form what is perceived as objective reality "(ibid.). that could be determined under the given conditions. In order to make it believable that the reference to terms

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70 Staudinger, who is considered the founder of macromolecular chemistry, was initially a general recognition been denied. Neither organic chemists nor colloid chemists responded to his ideas about polymer structures, especially since it did not appear to be particularly attractive at the time to deal with “lubricating chemistry” (see Staudinger 1961: 77). In the early 1920s, attempts were probably made to apply a new physical method to the problems of structure elucidation of organic high polymers. However, the use of this method, the X-ray structure analysis, led to contradictory results that spoke both for and against Staudinger's ideas.

there, 63). "It is (only) certain that genes cannot be" seen ", as Geitler saw in the late 1930s (1939: 144), and so of course all the properties in which one saw analogies to the virus types had to be found wanted to be hypothetical. It was still questionable whether genes are real at all or just fictions or unsubstantiated entities (see Morgan <1933> 1965: 315), especially since the paths to their empirical research were not certain, which could have been followed. "... the material used by genetics in the first half of this century (neither allowed) to examine the substance (the genes - KL) nor to investigate its mechanism of action," said Jacob (1972: 278). And Schrödinger (1951: 13): "After the rediscovery of the Mendelian rules ...

That is why there were of course a number of researchers who contested the similarity of the virus to the gene or the macromolecule. Darányi, for example, thought it absurd to see only macromolecules in viruses, “since a molecule is a chemical term and not a unit of life. The protein molecule is not alive. In order to be able to live, it must also contain other substances (lipoids, salts, carbohydrates, etc. - KL), although this does not significantly change its size ”(Darányi 1937: 1267). Doerr (1944a: 49) also opposed the giant molecule concept. It is absurd to interpret, for example, the causative agent of psittacosis as a giant molecule. "Not only the size of these elements ... would be incompatible with such a view, but also the ... high-level pleomorphism". And advocates of equating the virus with the gene were countered: genes can be found “in every living organism that reproduces and passes on its properties to its offspring. Virus proteins ... only occur in sick organisms. Posed in this way, the question of the analogy of these two elementary units is wrong, ”says Kausche (1939: 73). Doerr argued that researchers who maintained the virus's assumed similarity to the gene said they had "All objections, which oppose the identification of virus particles and genes, were attempted to be bridged by unrestrained towering of hypotheses" (1944a: 69).

Supporters of the microbial virus concept saw the possibility of using the genetic term of heredity research as a way to invalidate the argument given to them by their opponents that the miniscule size of the virus that could be filtered was incompatible with the complexity and quality of the organization commonly considered characteristics of living things. How could such a tiny particle as the virus contain all those substructures that are the bearers of the diverse life functions (breathing, assimilation and dissimilation, multiplication, inheritance)? Burnet and Andrewes indicated in 1933 that the individual virus particle of foot-and-mouth disease was no larger than 10-20 molecules of hemoglobin

can. They found it difficult to understand how a particle made up of so few molecules can be organized “to perform all the complex functions of a living, independent organism” (1933: 167) .71 The thesis that the virus Such questions now seemed to render the question of genes similar, meaning that as small as genes are, inheritance researchers gave them the rank of life units. They were shown not only as a mere component of the cell substance, but as a fundamental property of the living substance.72 At the beginning of the 1930s suitable objects (gametes from Drosophila melanogaster) were used to determine the diameter of the volume of the genes, ranging from the smallest to the smallest corresponded to medium-sized virus elements, with which there was a point of contact. According to Bail in 1925, certain peculiarities of the bacteriophage, which had been a problem for adherents of the living theory, could also be explained in the light of the concept of genes Organisms in the organism ”, as he writes (referring to an essay written by Muller in 1922). “This makes it possible to understand the peculiarities of the bacteriophage, which on the one hand appear to be similar to an organism and on the other hand lack important characteristics of such an organism”, such as the lack of independent reproduction (1925: 15). "It seems," says Darányi in 1937, "as if such a unit as a gene, virus, phag is generally the smallest unit of life" (1937: 1267). The analogous recourse to the gene concept was promoted by the fact that heredity research assigned a high degree of autonomy and stability to the genes, which was accompanied by a certain plasticity that was characteristic of all organisms. The genes could be caused to vary under artificial conditions (for example by irradiation), just as they vary spontaneously (mutation). And from a physiological point of view, the growth of the genes in the cells presented itself as an increase in individual units, in which something very similar to the virus increase could be seen. And that in the course of reproduction - judged by their phenotypic effects - the genes showed considerable toughness in preserving their properties, combined with a certain degree of variability,

71 At the same time, however, they reckoned with insurmountable difficulties in trying to “interpret all the complicated symptoms of the viral diseases as being caused by a non-corpuscularly organized agent” (ibid.).

72 "... a gene is a minute organic particle", as Demerec explains a few years earlier (1935: 271), "probably a single large molecule, possessing the power of reproduction, which power is one of the main characteristics of living matter. Changes in gens (mutations) are visualized as changes or re-arrangements within molecular groups of a gene molecule. "

73 "The mutations of the viruses manifest themselves in changed symptoms of the disease" (Melchers 1960: 97).

just like the genes in the organism "can initiate a reaction chain, at the end of which there is a manifest feature, the symptom" (Kausche 1940: 362).

Developments in experimental heredity research were also reflected in cancer research. First of all, the classic ideas of genetics came into play: One of the predominant themes was the idea that pathological cell divisions can give rise to cells that are still viable and capable of reproduction and have the properties that can be observed in tumor cells that it is possible that a factor exists within the cell that is significantly involved in tumor formation. At the beginning of this century, this factor was called "chromosome" (structures observed during core division). And so cancer was interpreted as being dependent on malformed chromosomes in the cell nucleus (see Boveri 1914; ders., 1929). Specifically, this approach (described as the “somatic theory of cell mutation”) says something like this: Chronic irritation causes a certain change in the chromosome content of the cells, which results in the abnormal proliferation, the emancipation of the tumor cells from the other body cells, the Change in cell function to explain the inheritance of the new properties to all cells newly created from such cells. When later the genes lying on the chromosomes were supposed to be the carriers of the hereditary system, instead of the entire chromosome as a single entity (see Sutton 1902; note from: Jahn et al. 1982: 465 f., 737; Boveri 1909), could cancer formation, based on the general idea that it was an irreversible change in the inheritable characteristics of a cell, can now be seen as a mutation of genes. Genetic transmission of tumor features has been envisaged. 74

Those researchers who favored the notion that the virus was not a living organism but an enzyme-like substance and that one day it would be possible to obtain a chemically pure virus hoped to gain knowledge, particularly from advances in macromolecular chemistry on the virus nature (see Schmidt-Lange 1943: 711). Although it was a matter of debate that the viral proteins, like those of other protein bodies, were composed of a number of the same subunits, there was no consistency in the structure, size, and mutual relationship of the units. In the early decades of the 20th century, biochemistry was largely based on the colloid and aggregate theory of living proteins, which said that proteins and proteins in the protoplasm of living cells exist as aggregates of small molecules. There was a widespread idea that the colloidal stage of protein compounds should be viewed as a specific feature of living cells, to which chemical laws were not fully applicable. And so there was no reasonable reason at the time for the physiological processes of the cell, the intracellular phenomena and the function of the cell nucleus or its material.

components consistently based on chemical laws (see Olby 1974: 19). For the theory of endogenous virus production, an increase in plausibility could be expected if it were actually possible to represent some types of virus in the form of macromolecular proteins, that is, proteins whose large molecules in solution state can be identified with the virus elements . The assumption that viruses appeared spontaneously in host bodies without exogenous infections became more attractive after Stanley succeeded in rendering the tobacco mosaic virus in crystalline form in 1935. The virus presented itself to him as something that behaved like a chemically pure protein in all its properties, which contradicted the understanding of the virus as a living being. Isolated protein molecules could be denied the ability to nourish, multiply, inherit and adapt. Organisms were generally denied the ability to crystallize. It was pointed out that the structure of a crystal lattice presupposes a large degree of agreement and a great regularity in the structure of the individual particles, but the chemical composition of the agent should, if the living being theory is correct, be subject to a certain variability or Virus particles should have a certain heterogeneity.

With the borrowing of terms found outside of virus research, the gap between the different groups in this research direction was not immediately narrowed. The fronts hardened even more, and there was a collision of genetic and biochemical "areas of experience" when interpreting and researching the

74 However, as Hildebrand corrected in 1939, this concept could not match the long latency in tumor formation after contact with chemicals. How could a mutation that meant an immediate change be consistent with the slow development of tumors? Hildebrand attributed the conversion of a normal cell into a tumor cell not to a somatic mutation, but to a permanent modification, to a change in the cytoplasmic cell components, caused by a stimulus that attacks the cell plasma and not on the cell nucleus. With the assumption that the malignant conversion of a cell was based on a somatic mutation, i.e. a gene change, there was no evidence that that carcinoma development in the skin when the mouse is brushed with a tar solution takes place in such a way that the uppermost cell layers (epithelia) of the deeper layers of the epidermis gradually take on the character of malignancy over numerous cell generations, and that the transformation into a carcinoma cell in many epithelia takes place simultaneously , that is multicellular and multicentre. However, gene mutations always take place in leaps and bounds. This was precisely what Hildebrand could never find in the malignant transformation of the epidermal cells (Hildebrand 1939: 395). that is, multicellular and multicentre. However, gene mutations always take place in leaps and bounds. This was precisely what Hildebrand could never find in the malignant transformation of the epidermal cells (Hildebrand 1939: 395). that is, multicellular and multicentre. However, gene mutations always take place in leaps and bounds. This was precisely what Hildebrand could never find in the malignant transformation of the epidermal cells (Hildebrand 1939: 395).
Also of interest in this context is the debate at the time about whether there might be a relationship between the agents of the filterable chicken sarcoma and the genes of the nuclei of certain chicken cells, that is, whether the rous agent is genetically from the core genes of the chicken cell had to be derived, so the rous agent was a malignant (mutated) gene in the chicken cell. On the other hand, the incompatibility of the results of Gye's duck trial mentioned above with Fujinami sarcoma could be cited. Graffi, referring to certain experiments, says that the nucleus and thus also the individual nucleus genes are autonomous with regard to the species specificity. The genetic mass of a nucleus retains its original species specificity in all circumstances in the alien plasma. If the agent of the chicken sarcoma were to be derived genetically from the hereditary mass of the cell nucleus (genes), one would have to expect accordingly that the Fujinami sarcoma would keep its chicken specificity constant also in the duck cell. However, according to Gye's experiment, the serologically ascertainable species specificity of the agent had changed from chicken specificity to duck specificity (Graffi, loc. Cit., 545).

Virus origin and effects.75 And yet this initiated a development, in the result of which the controversial questions became irrelevant. Turning to the “macromolecule”, the question of whether the virus was a “contagium fixum” or something soluble appeared in a different light. In the light of advanced colloidal chemistry, both versions had something to offer. If one could say that the virus was in a molecularly dispersed state, then the alternative - liquid contagion or corpuscular pathogen - could be understood as a consequence of the now overcome state of development of colloid chemistry in the 19th century. Neither the equation of the tobacco mosaic virus with enzymes (Woods 1899) nor the understanding of the virus as a pathogen that is external to tobacco plants (Ivanovskij 1902) can be wrongly assessed in retrospect (see Wegmarshaus 1985: 78 f.): From a material point of view Both enzymes and viruses are proteins, albeit with different molecular weights, and viruses are protein bodies with an RNA or DNA component, but not a plant-specific enzyme. The virus is actually a corpuscular agent. Based on colloidal chemical considerations, Beijerinck's thesis of liquid contagion also had something to offer albeit with different molecular weights, and viruses are protein bodies with an RNA or DNA component, but not a plant-specific enzyme. The virus is actually a corpuscular agent. Based on colloidal chemical considerations, Beijerinck's thesis of liquid contagion also had something to offer albeit with different molecular weights, and viruses are protein bodies with an RNA or DNA component, but not a plant-specific enzyme. The virus is actually a corpuscular agent. Based on colloidal chemical considerations, Beijerinck's thesis of liquid contagion also had something to offer

- The virus was in a molecularly dispersed state. In the light of changed conceptual guidelines, neither the organism nor the molecular hypothesis could be fully supported for longer.76 “The word organism demands”, says Bawden (1964: 12; note from: van Helvoort 1994a: 217), "a wealth of independent metabolic activities there was never any reason to assume viruses possess, and the word molecule implies a precise knowledge of chemical composition impossible to get with particles as large as viruses, and demands an unchangeable structure that conflicts strikingly with the great mutability of viruses. "

With the said equations, initially only symbolically mediated transformation relationships between different areas were created, which, however, uncovered a new development potential for the empirical processes, for processes that led to operational coherence of previously independent areas of experience. There was a transfer of methods and processes (see Kay 1993: 5), a transfer with which the previously assumed equivalence of virus and macromolecule, for example, was to be established practically.77 That in the case study dealt with at the linguistic level initiated convergence of research directions from different disciplines to continue them on a research-practical level becomes clear, for example, in an essay by Kausch from 1940: He writes that,

75 “The biologist who regards the viruses as living studies them in living hosts where they behave as organisms; the chemist who considers them chemicals studies them in the test tube where he sees only their chemical

and physical properties ”, says Chester in 1947 on the situation in virus research (1947: 313, note from: van Helvoort 1993: 24).

experiments “according to the strict definition of genetics” lead experimentally to the consequence “that one has to 1. try to causally determine the specific properties, ie the mode of action or the success of a virus protein, with its defined physicochemical constants link; 2. Studies on analogies between the gene and the virus aim to change the effect of the virus protein through visible interventions so that it can be demonstrated physico-chemically. To do this, the end link of the reaction chain, namely the symptom picture, must first be manifested in a changed form and paired with a change in the physicochemical properties of the active body.

76 And in phage research, neither d'Herelle's position nor that of his opponents could be maintained without restriction. Virus multiplication was not comparable to the growth of a bacterium in a nutrient medium or the direct conversion of an inactive "precursor" into an active enzyme, which Northrop had assumed. When it was possible to demonstrate that the substrates being handled were free of the lytic agent, and when it was possible to prepare concentrated phage suspensions free of admixtures after using high-speed centrifuges, improved methods of turbidity measurement, isolating viruses as descendants of a single virus particle and using other means, after the phage had become a molecular genetic object (at the beginning of the 1940s) and examined independently of therapeutic objectives - an object that could not have been treated as a molecular genetic object either by lysis experiments or by simple genetic experiments (Doermann 1972: 95) -, a starting point was gained regardless of the positions represented in that controversy, which in my opinion is expressed in the following Delbrück quote: "In d'Herelle's view the bacteriophages are small cells, in Bordet's view they are modified bacterial proteins. The issue is one which can only be settled by a clearer understanding of what actively goes on when the bacteriophage is reproduced. The experiments which have been devised in the attempt to settle this argument have not yet led to a clearer understanding of the mechanism of phage reproduction ”(1942: 2). Ellis, who had worked with Delbrück at times, still seemed to come close to d'Herelle's description of the phage multiplication process "the picture we have today" (1972: 62). But d'Herelles was not at all concerned with investigating the propagation process itself, but this was necessary to clarify the molecular basis of the propagation. A different picture emerged, however, by examining the phage multiplication process separately from the multiplication of the phage hosts and questions of antibacterial therapy (see Delbrück 1946: 174 f.).
“The phages could no longer simply be viewed as extremely small intracellular parasites like it was d'Herelle, who preferred analogy considerations ”. The "weaknesses of the analogy were that it could not explain the lack of metabolism in the particles ...", says Hershey (1972: 108).

77 Based on Stichweh, the coexistence of heterogeneous knowledge systems - it refers to the developmental relationship between physics and electrical engineering - can be characterized as an interpenetration process, for which the instrumentation or experimentation technology functions as an “interpenetration zone” (Stichweh 1988: 702). The different cultures of knowledge connect to events in this zone in different ways and transport them into divergent horizons of meaning. Finally - as a result of the development of interdisciplinary transport - the difference disappears in the new objects.
Molecular biology “would borrow methods not only from physics, mathematics, and chemistry but also from other fields of life science - genetics, embryology, physiology, immunology, mi-crobiology. The new biology aimed to transcend disciplinary boundaries and employ whatever tolls the problem at hand demanded. Although the transfer of techniques between fields was certainly not new, the design of a large-scale program based on interdisciplinary research encom-passing several disciplines was unprecedented ”(Kay, 1993: 5; see also 136 ff.).

remain constant ”(Kausche 1940: 362 f.). The fact that borrowing has consequences in methodological and other respects in the borrowing direction of research can also be shown in view of the consequences that were conjured up when it was agreed to equate viruses with macromolecular nucleoproteins: For example, with the efforts that To make the hypothesis of endogenous virus formation plausible could no longer be satisfied with the assumption that a structure of the host cell consisting of nucleoprotein would be converted directly, that is, without chemical transformation into a virus element. The idea was biologically intolerable, “that a particle belonging to the host cell can be affected by the influence of this cell directly or without changing its dimensions,

With the borrowing of concepts from other disciplines, the associated research problems also had an effect in their own specialist area, and there was pressure to orientate themselves in their own investigations to the procedures and questions of the foreign discipline. Because for a convincing presentation of concepts of foreign communities as something that belongs to the prerequisites, the guidelines of one's own fact production, the research results have to be presented as something that can also be assessed and reconstructed in the reference system of the respective community. As a consequence, this means that your own experimental and observational findings must be translatable into those of the community whose concepts have been used. This is the only way to make it believable that such a reference was the necessary prerequisite for the achievement of the research objectives and was one of the observation conditions of the research subjects dealt with. One can assume - which has to be checked by further analysis of the historical case study - that the controversies in virus research have become pointless to the extent that from the initially assumed suspicion of similarities between virus on the one hand and the gene, considered in the debates , the macromolecule, etc., on the other hand, implications were drawn from an empirical and practical point of view, as a result of which virus research, even in the laboratory, emerged from the spell of conventional approaches with which the problems of explaining the nature of the virus could not be overcome.

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