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What is a “scientific fact”?
A small case study: “the measles trial”

In the last chapter of the series on methods, we saw from the replication problem that has plagued medical science and now psychology that a single study, even if it is well published and well publicized, does not turn into a fact. The data must also be replicable, ideally by independent researchers, ideally by other groups with the same or a similar method. Would that be enough?

No. I have indicated and often explained on several occasions: science is a social process. And an essential part of what is scientifically accepted depends on the consensus of a community of researchers and specialists. Ludwik Fleck was the first important scientist who pointed this out in the 1930s. He showed how difficult it actually was to identify a syphilis spirochaete, i.e. the bacterial pathogen of syphilis. Using this example, he was able to demonstrate how crucial social processes are in establishing scientific consensus.

A summary of his point of view is the following one-liner: "A scientific fact is the general agreement to stop thinking."

I want to illustrate this by using a fascinating example: the ongoing "measles virus trial" and the question "does the measles virus really exist?". Yes, that's a bit like the assertion "Bielefeld does not exist". But even that had its meaning.

Introduction

The dispute of the so-called "measles virus trial" is whether Dr Stefan Lanka owes Dr Bardens the prize money of €100,000, offered as a reward by Dr. Lanka in an advert "only if a scientific publication is presented, in which the existence of the measles virus is not only claimed, but also demonstrated, including among other things its diameter. "[1] Dr Bardens submitted six studies, of which he believes that they meet the criteria. Dr Lanka rejected them. In a civil trial, Dr Bardens sued Dr Lanka and Dr Lanka was ordered by the court to pay the prize. The defendant, Dr Lanka has now lodged an appeal.

This is a very interesting situation: A single person, who is qualified in the matter, challenges the consensus of the majority. He does this with the help of a challenge in the form of an advertisement of reward; otherwise no one would be likely to respond to it. At this point we can already ask ourselves: how useful is this advertisement - beyond the intended challenge? Can it ever be possible, in principle, to try to prove a fact by means of a study? I can cut a corner here for impatient readers: In principle, this is not possible in my view. Nowhere. Not in any field. The measles virus trial is a good illustration of this.

The question to be clarified, therefore, is *whether the submitted papers (see details below) are scientific papers which qualify to provide evidence for a measles virus*. Out of personal interest, I examined the six papers, because I find this discussion fascinating and I want to express a few thoughts.

This already implies (to avoid misunderstandings) what is *not* the subject of this article:

- It is *not* about elucidating whether measles exist or do not exist. Of course measles exist as a clinical and pathological entity.
- *Nor* is it about clarifying whether measles are triggered and caused by a virus or not,
- and *it is certainly not* about whether the measles vaccine is effective and meaningful.

Well, what is "scientific" in this context?

The concept of scientificity

Scientificity is a complex construct. The fact that a text is published in a scientific journal says no more and no less than that competent readers and colleagues understand the text, considered it to be good and correct and that editors and reviewers of the journal found the text to be of interest for their readership, usually a professional audience. It doesn't say anything about the truth and validity of, nor about the quality of the information published there. To this effect, all but one (details below) of the papers submitted in this trial are "scientific". They comply with the minimum standards of having been published in a scientific journal.

However, the consensual, social acceptance belongs to the concept of science as well. This is not a criterion of truth either, but a sign of indisputability. Controversial opinions are generally not considered "scientifically accepted" and are not referred to as "scientific", but are often dubbed as "unscientific" by the opponents. This usually means "an opinion not accepted by the majority of people who work in a field".

If something is generally accepted scientifically, i.e. with no notable and especially socially superior disagreement, it is usually adopted as a "scientific information" in textbooks and in the public opinion. Minority opinions are then often marginalized and ignored until someone manages to express objections from a comparatively prestigious position and opens the debate again.

In this regard, the assertion "Measles is caused by the measles virus" is undoubtedly a scientifically accepted opinion, which also implies that there is a measles virus and that this virus has been demonstrated to be a causative agent. That is why the view expressed by Dr. Lanka, that this "scientific fact" came about from a misconception and by poor methodology, is a minority opinion, which would be described by the majority of scientists as "unscientific." The expert opinion issued by Prof. Podbielski, the expert appointed by the first court, implicitly follows this reasoning.

Well, the majority opinion, particularly in science, is not a sufficiently good guidebook, even if it is more common to us than an individual, isolated analysis, since we humans are social beings, and scientists are social beings as well. Many historical examples could be cited to prove why majority opinions are wrong. Here are some examples:

Already in 2004 Dean pointed out that the mono-causal thinking in medicine is actually obsolete, especially in infectiology, because the vast majority of infections only develop as an interaction between pathogen and host [2]. However, because it is easier to focus on the pathogen, the complexity is overlooked and mono-causality continues to be imposed as scientific standard, in an act of unaccountable abstraction.

In astronomy, the doctrine that no planets existed outside our solar system was considered scientific standard for a long time. Many astronomers had poor promotion prospects if they did not adhere to this dogma. Today several hundred additional planets are known.

During the Nazi regime, a majority opinion of German doctors and geneticists advocated the racial ideology, which attributed a genetic, medical or another inferiority to non-'Aryan' races. This scientific opinion disappeared in the twinkling of an eye after 1945 – suddenly considered untenable.

A more detailed analysis of the nutrition debate, especially in the US, shows that the theory of the dangers of saturated fatty acids (claimed for decades) and superiority of unsaturated fatty acids in disease prevention and maintenance of the standard weight, which was the majority opinion and part of official position papers until now, is currently collapsing under the burden of contrary data, which had

been long known but ignored. The social exclusion mechanisms of the academic establishment had determined that minority opinions, well founded as they may be, were not listened to. [3]

Generally, one can see that vital discoveries come more frequently from the edge of the accepted establishment than from its center. [4] The other way around, it is well know that economic interests often make use of well-positioned outsider opinions to sow doubt and slow down changes that are actually scientifically well documented, as in the question of whether smoking causes cancer or whether human activity is responsible for global warming. [5]

The same principle applies of course the other way around: if, as in the health sector, the economic interests are very strong, very obvious facts are often overlooked, because all parties react with perception denial, for a different view of things could offend crucial loyalties and interests. [6]

In this respect, in all debates on "science", including this one, one should not forget to look at the social, economic and historical context of the concept of science being used and of the values associated with this concept.

The methodology depends on social acceptance and historical realities and needs to be revised

The following connection is also often being overlooked: there cannot be a scientific method that could be asserted forever. New methods allow new insights, invalidate old insights or render them more precise. The experimental method which is mainly at issue here is a powerful method, which has been practiced for a long time. However, this method continues to be improved. For example, in the past a simple control was sufficient for a scientifically acceptable publication. This applies to the first three of the papers in question. Meanwhile, the standard requires that controls are randomized and in many fields double-blind experiments are necessary. As Sheldrake has found in a survey, randomization is not usual in the biological, medical and physical basic research. [7]

While in parapsychology approximately 85% of all experiments were blind, in the basic medical research only 6% of all experiments were blind. This shows that methodological rigour often also depends on whether the experimenting researchers are aware that in their field the experimenter risks influencing the results through his opinion and attitude. Rosenthal has clearly demonstrated this by his experiments in psychology and, analogously, for the medical science as well. [8]

Therefore, in clinical medical and psychological experiments randomization is common, but hardly in basic research. "Why should it be?" says the involved researcher to himself, "we measure objective data". But even such measurements and perceptions may be desire-driven, as Fleck was able to show using the example of the serological Wassermann reaction. [9]

Meanwhile, new standards are being recommended, but they only become accepted in some areas of expertise, since they are complex and expensive. This is the case for systematic, negative controls. A systematic, negative control means replicating an experimental procedure in all details, without introducing the putative causal agent; i.e. if, as we shall see in this example, the experiment consists of growing and treating a cell culture in a particular way, placing a nutrient solution and finally the suspected causative agent into the cell culture as well, a systematic negative control would subsequently consist of creating an independent control group for each single step of the experiment. It would be the only way to see if only the [suspected] causal agent is responsible for the obtained results, and not possible artifacts.

This form of control has been, to my knowledge, introduced by Jan Walleczek and his group [10]. It has, however, not spread very much, because it is expensive. Interestingly, it is mainly used by researchers who work in fringe areas of science. [11]

To my knowledge, the most accurate studies from an experimental medical field with systematic negative controls have been performed by Garret Yount. [12] Johrei-healer, a Japanese group who claimed to be able to use "Ki" (an intangible form of energy) in order to modify cancer cells were examined. Because initial pilot tests had been positive, the researchers decided to investigate thoroughly. Cancer cell cultures were set up and "healing intention" was applied by Johrei-healers, in particular by a master. In systematic negative control experiments, the whole setting was carried and set up identically. A person was placed at the same distance and for the same period of time, in order to detect any possible temperature or electromagnetic effects. The control experiment took place at the exact same time and place, at the same temperature and the same humidity. Systematic negative controls were also carried out without any person, only to detect the time factor and the variability of the system. By means of all these controls, the initial positive results have been documented as not stable enough and the "healing effect" was exposed as an artifact.

From this example we can conclude that, generally, theoretical models which are less accepted by the scientific community have to go through much stronger controls in their experimental investigation. As a rule, the severity of the control depends on the *a priori* certainty (derived from theoretical model assumptions and unsystematic experiences) about how probable a particular fact is. In this respect, this is always determined by historical factors and indicated by the momentarily prevailing mainstream. If the general attitude is open-minded and positive, less strong data suffices to convince the majority of researchers. It is then that important controls are often omitted.

What is "scientifically proven" is therefore dictated not only by the method used, but also by the interaction of a currently prevailing model with methodological considerations and with *a priori* considerations on the likelihood of a presumption due to other findings, due to the prevalent views and due to a background theory.

From the above it results that *a single* experiment, *a single* publication can never ever offer total certainty and even less establish any scientific fact. This happens rather in a complex exchange process, in which important papers become the sources of discourse: they are being replicated, they are being criticized, they are being commented upon. And at the end of a complex social negotiation process among professionals - which takes place mostly in discussions and not in writing - a "scientific fact" emerges.

Therefore, one can see the advert for reward only as a challenge calling upon the scientific community to reflect. It is interesting to see how mainstream people react to this challenge by Dr Lanka. Let us have a detailed look at the studies.

The Papers

Study no. 1

Enders, J. F. & Peebles, T. C. (1954) Propagation in Tissue Cultures of cytopathogenic agents from patients with measles. Proceedings of the Society for Experimental Biology and Medicine, 86 (2): 277-286

This study reports on an experimental investigation of seven children who had been clinically diagnosed with measles. Throat washings, venous blood and feces were taken from these children and further processed biologically. These were then treated by appropriate methods, until it could be assumed that bacteria could have no longer been active. The substances were centrifuged and treated with penicillin and streptomycin. In addition, 2-ml of sterile, neutralized, fat-free milk were added. Then, the solution thus obtained was introduced into different cell cultures, the transformations were observed microscopically and compared to untreated cell cultures. The authors discover pathological changes,

showing enlarged cells and suggesting a “migration” of a foreign substance into the nucleus, so that the chromatin, i.e. the chromosomes and the surrounding histones are pushed away. In addition, inhibitory effects could be observed when the infectious isolate was heated, introduced into other cells and then added to the infected cells. Cooling, however, does not affect the infectivity. This suggests indirectly that the foreign substance must be a protein.

The authors evaluate their findings as preliminary: “It is our purpose to describe here these observations in a preliminary manner. Additional evidence ... will be sought in future investigations” (p. 278). At the end of their paper they describe the data as “indirect evidence” (p. 286). This indirect evidence should be supplemented by two additional experiments which would have to be carried out: the direct causation of measles in monkeys and in man with tissue culture materials.

Methodological remarks and comments:

The study was carried out with material from 7 children, all of whom were clinically diagnosed with measles. Infectious material could be isolated from 5 children. The material obtained from one child’s throat washing did not lead to the cytopathogenic changes which were observed in the material of the other 4 children. Thus, there was no 100% infectivity. The authors doubtlessly tried to avoid mistakes, within the limits of the then valid knowledge. Thus, they attempted to treat their fluids by adding antibiotics, in order to exclude as far as possible any bacterial causation of cytopathogenic effects. However, according to today’s knowledge it is still possible that resistant strains survived and multiplied in the relatively prolonged incubation period (14-21 days, p. 281). However, the inoculum was filtered through micro-filters which can retain the bacterium Serratia marcescens and the filtrate, the authors say, was free of bacteria, which they were able to show by negative growth experiments. Therefore, it is plausible to assume that no bacteria, at least none that was known at that time, is responsible for the infectious changes.

However, as the authors themselves state, it is possible that other infectious agents in monkey tissue could be responsible, because only monkey tissue has been consistently shown in this and other attempts to be suitable for propagating infectious agents: “only those in which monkeys were employed as the experimental animal have been consistently confirmed by other workers. Great caution should therefore be exercised in the interpretation of any new claims that the virus has been propagated in other hosts or systems. "(p. 285)

Thus, the authors advise caution, and rightly so. Whether the shortcomings noted by the authors themselves have been corrected in later studies by the authors or by others is not the subject of this analysis. Apparently, the observations were confirmed by other authors, as study no. 2 reports.

In addition, it should also be noted that the fluid used for the experiment was treated with many substances - sterilized milk, antibiotics, trypsin, etc. -, but a control fluid containing the same substances without washings or sera from blood or stool was not used. Insofar, even if the control experiments are very convincing, they are not really equivalent. A systematic negative control was not carried out. It is only fair to mention that this strict control was only established over the past few decades - thus, the authors performed a “tidy” job by the then applicable standards, otherwise the work would not have been published in a scientific journal. However, this study cannot constitute explicit evidence that the smear or the sera may have solely caused the observed changes. At best, it is suited to be a tessera (small piece) in a larger picture.

It is also important to note that the authors use the term “virus” in this text with its old Latin meaning as “infectious agent” or “poison”. For this reason, they also speak mostly of “infectious agent” or “etiologic agent”.

Synopsis: the study shows that cellular modification processes can be induced in cell cultures using

material from throat washings and blood of children who are clinically ill with measles. But, on the one hand, this does not happen with all materials. On the other hand, it takes a relatively long time of 2 to 3 weeks. In addition, it cannot be guaranteed by the design of the experiment that what is truly responsible for the changes is only an infectious agent from the material of the sick children and not some characteristics inherent to the studied monkey cells which appeared due to the treatment. Finally, from today's perspective it cannot be excluded that the observed changes were caused by resistant micro bacteria. The term “virus” is used here figuratively. Therefore, this study cannot provide proof for the existence of a measles virus, but at best a piece of argument in an inevitably more complex reasoning.

Study no. 2

Bech, V. & Magnus, P. (1958) Studies on measles virus in monkey kidney tissue cultures. Acta Pathologica Microbiologica Scandinavica 42 (1):75-85.

This study mainly replicates the findings of Enders & Peebles (1954) and reports on two other replications, which were said to have taken place in the meantime. For the purposes of this article, it is relevant to note that the methodology was essentially repeated. The difference is that the specimen obtained from washings or blood was stored or cultured in another culture and suspension media. Penicillin and streptomycin were used again as antibacterial substances. The isolation of the infectious agent, which in this publication keeps being reified and referred to as “virus”, was achieved out of throat washings or by gurgling with infusion broth or from blood. The following observations are important for further consideration at this point:

- 13 patients were examined, 5 of these showed positive reactions (“virus recovered”), the other 8 did not.
- Only in one of 11 patients could a cultivation from blood be established.
- The alleged correlation which the authors claim with respect to an easier detectability of material collected at an early stage cannot hold: In 3 of the 5 established agents the infection dates back 24 or 18 hours, in 2 persons the time period is shorter. This is in opposition with the negative findings in the 2 other patients from whom material was collected less than 24 hours after infection.
- The cytopathic changes reported seem to appear in uninfected tissue of monkey kidney as well and can therefore hardly be called pathognomonic, which incidentally was described by the other authors as well: "cytopathic changes similar to those caused by measles virus may be observed also in un-inoculated cultures of monkey kidney tissue (Fig. 4-5). These changes are probably caused by virus-like agents, so called ‘foamy agents’, which seem to be frequently present in kidney cells from apparently healthy monkeys” (p. 80).

The latter observation seems especially remarkable to me, since it refers to the un-specificity of exactly those pathological changes which in the first publication of Enders & Peebles served as a starting point for the visual proof of an infection.

As proof of the correctness of the assumption that it was a “virus”, it is argued that a “complement fixation test” was positive. This was performed on a total of 4 patients. Under the plausible assumption that the patient numbers reported in Table 2 refers to the patients originally reported in Table 1, this means that among the 4 patients there were two from which originally no virus could be isolated, in one patient this was successful and the fourth patient was a new patient. It remains unclear in how many patients this fixation test was carried out with negative results or why the test was not performed in all patients.

Enders & Peebles had cautioned that only an experimental production of illness in monkeys or humans with tissue culture material could prove the causality. Therefore, in this study an infection experiment was performed on two rhesus monkeys born at the laboratory. One of the monkeys showed subclinical symptoms. A corresponding antibody titer was said to be observed in both.

Methodological remarks and comments:

The study presents in principle the same weaknesses as the original study by Enders & Peebles:

- It is possible that the changes were caused by resistant bacterial strains, not covered by the antibiotics.
- There is the possibility that some substances in the solution medium are responsible for the changes.
- It is possible that an interaction between the solution medium and monkey cell leads to the observed change.
- The rate of 5 patients out of 13 is below 50% and therefore far away from the Koch postulate of a 100% infectious causality. [13]
- The transmission of the disease to the monkeys succeeded in one of two cases. An antibody titer was detected in both monkeys; a previous infection with measles was excluded. However, this statement loses credibility next to the statement that a "foamy agent" in the simian kidney cells could just as well be the determining factor for the change, because it also cannot be ruled out that this same "foamy agent" - which is naturally present in monkeys - could have led to the detected antibody response.

From a linguistic perspective, it can be stated that in the course of one year and with three cited papers published in the meantime, the opinion that the infectious agent is a "virus" is now being postulated here as self-evident, since the authors speak only about the "virus". This is an interesting example for the way one uses certain terms to create reality, instead of the other way around.

In summary, this study cannot substantiate that there is "the" measles virus. What the study shows is that there is an infectious agent that can be detected in less than 50% of cases, but which could have just as well already been present in the cells. Also, and this was overlooked by the authors, it could have also appeared anywhere in the culture medium or through an interaction. This could have been ruled out only by systematic negative controls, which were not usual at that time.

Study no. 3

Nakai, M. & Imagawa, D. T. (1969) Electron microscopy of measles virus replication. Journal of Virology, 3 (2): 187-197.

This study provides a description by electron microscopy of the infectious agent in question, already named "measles virus" in this paper. At the beginning, it describes earlier papers, which mentioned diameters in a range of 100-150 nm and 120-250 nm, respectively. In this study, the different stages of the viral replication are to be described. For this, the so-called "Edmonston strain" of the virus "propagated in HeLa cells [14]" is used. The indicated literature for this refers to the original paper by Enders & Peebles (1954), Study 1 above. The harvesting of the virus is not described; the publication offers two interpretations for this: 1) The original isolates from Enders & Peebles, which had at that time been introduced by them in cell cultures, were used here as well. 2) The methods used by Enders & Peebles for collecting infectious material were used here as well. It is difficult to say which of the two interpretations applies. The cells were incorporated into new HeLa cells, treated with various reagents, further cultured and purified in four increasingly long centrifugation steps, apparently based on the idea that at the end the lightest particle, the virus, would be left in the filtrate and this way it would be

available for inspection under the microscope. Several variously shaped structures have been found ("the virions are pleomorphic", p. 189) which exhibited very different sizes between 180-600 nm.

Treatment of controls is not mentioned. With regard to this, the paper only mentions: "Control preparations of un-inoculated HeLa cells were examined in a similar manner" (p. 188). This can be construed as meaning that the untreated HeLa cells were subjected to a similar stepwise centrifugation and were examined microscopically. However, this can also be construed as meaning that the control cells were treated with the same reagents, as defined by a systematic negative control. Since this is not further mentioned, and we suppose that it would have been mentioned, since it would have been indeed a complicated production step, we cannot assume that such systematic negative controls have been performed. There is no report on the findings in control cells. The pictures show only experimental cells, no controls for comparison.

The authors write that the cytoplasmic inclusion bodies that they observed, i.e. inclusions in the cytoplasm of infected cells, could be related to the formation of new viral particles, but call this a speculation, which must be confirmed by similar examinations with a clear immunological marker. The same applies to nuclear inclusion bodies. It is unclear how these relate to a possible viral replication: "The relationship between the nuclear inclusion body and the replication of measles virus is not clear." (p. 196)

Methodological remarks and comments:

The validity of the study is based on three requirements that are not clear in the context of the publication:

- The study makes the assumption that the method used by Enders & Peebles is appropriate for the isolation of an infectious agent; at least, this is the study given as a reference for the isolate. There were no further details with respect to the methods of isolation. This may be because the extraction method was generally accepted at that time, or because it was simply applied here. It remains unclear whether the agent was isolated during this study or if they used the one grown in cell lines since Enders & Peebles, i.e. for the past 15 years.
- The study assumes that from a new culture of the infectious agent and after filtration or centrifugation only the infectious agent is isolated.
- The study assumes that the reagents added to the HeLa cells for the preparation of the specimens are irrelevant.

It remains most notably unclear how the supposed virus was grown and then multiplied in the cells. The wording of the authors ("The Edmonston [15] strain of measles virus [6 - this refers to Enders & Peebles 1954; paper 1 above], propagated in HeLa cells, was used in this study." p. 187) does not contribute to any clarification. This is the only statement regarding the method of extraction of the infectious agent.

A systematic negative control, i.e. a control condition that was treated the same way as the experimental cells, including staining, incubation etc., seems to have not taken place. In fact, apparently some untreated cells were simply inspected. It is not mentioned what happened to the control cells exactly. The paper mentions nothing about whether structures of a similar nature were found in the control cells or not.

Incidentally, the size variance of the detected structures seems remarkable: previous studies report a size of 100-150 nm and 120-250 nm, respectively. In this study, particles of sizes between 180-600 nm were found.

Summarizing, despite the suggestive references and images, these studies provide no rigorous proof. To this end, a systematic negative control should have been performed and it should have been clearly reported that in these controls no evidence whatsoever of similar particles was found. Now, of course, an advocate may say that this was self-evident and therefore not worth mentioning. Although such reasoning is understandable, for the sake of rigorousness at least one sentence in this respect would have been necessary. It is unclear where the infectious agent originates from or exactly how the controls were treated and it is not clear whether anything in the controls became apparent and, if so, what this was. These facts together turn this study into an argument without any merit.

Publication no. 4

Lund, G. A., Tyrrell, D.L.J., Bradley, R. D. & Scraba, D. G. (1984) The molecular length of measles virus RNA and the structural organization of measles nucleocapsid. Journal of General Virology, 65: 1535-1542.

In this study, the RNA structure of the measles virus is to be examined by electron microscopy. For this, a virus strain was grown and introduced into cells. The cells were then incubated for 72 hours and after 90-95% of the cells had shown clear cytopathic effects, they were subjected to a purification procedure. From the resulting solution, the suspected virus isolate was extracted and then further investigated. For this purpose, the supernatant was treated and centrifuged repeatedly, in the ideal hope that only the virus is left. The result was examined by electron microscopy, in order to be able to determine the structure, size and shape of the viral RNA.

A part of the investigation consists in an electron micrograph of a representative virus (fig. 3a). The authors state that the variety in shape and size ("pleomorphic", p. 1537) already reported by Nakai & Imagawa (1969) was observed here again. While Nakai & Imagawa (1969) reported about sizes of 180-600 nm, in this study the particles found were between 300 and 1000 nm, i.e. approximately 1.5 times bigger than what Nakai & Imagawa had found. The virion shown on the electron micrograph has a size of 500 nm, which is about in the middle of the range.

Furthermore, the authors examined structures visually, performed length measurements and determined the fine structure of the nucleocapsids, i.e. those protein structures containing the viral RNA. The authors calculate the shape, length and amount of RNA inside a virion, which is not further significant for our analysis.

Methodological remarks and comments:

There is no report of control experiments in this paper. At a first glance, this seems not to be necessary, but it reveals, however, the potential flaw of the entire sequence of arguments. This paper is based on the assumption that a virus can in fact be isolated by infection and cultivation and then be characterized and further studied. If this assumption is correct, then the shape, size and polymorphism of the measles virus reported in this study are indeed documented. If the assumption is wrong, then the properties reported in this study belong to other particles.

This demonstrates that this paper, as is common practice in science, is based on the cumulative truth in literature, i.e. on previous experiments and papers. This is time-saving and, in a way, reasonable, but it also obviously increases the error dependence. Assuming, at first purely hypothetically, that in the reported procedure it was cellular particles from cells that had been extracted and further cultivated, then all analysis would relate to such particles, which subsequently would be (mis)construed as viral particles. Such an error could only be excluded by a single systematic negative control, i.e. a control procedure replicating all steps (nourishment, incubation, staining, adding of reagents and nutrient solution) *without* the initial inoculation with presumably infectious material. This did not happen, at least not in the paper discussed here.

Therefore, theoretically it is possible that what is seen here is not a virus from the measles isolate, but for example one that had already been present in the cell lines and was then further cultured in the cell lines, or a mixture thereof. Since the observed particles are “polymorphic”, i.e. they can have many forms and also very different sizes, the question whether a particle can now be assigned to a particular virus population is probably not so easy to answer.

This debate reminds of the one reported by Ludwik Fleck, which has established the syphilis spirochete as a fact only based on the Wassermann reaction and various staining techniques [16]. Fleck came to the conclusion that a scientific fact was an agreement. Similarly, here as well one can assume that there is an agreement that the particles found should be named measles virus. However, an “objective”, methodically independent fact is thereby hardly established. For this, several important requirements should have been met in this paper - or in previous papers, on which this one is based -, which are not to be found in this text:

Systematic negative controls should have been carried out in order to verify that the grown, cultured and propagated particles actually come from the virus isolate and not from the cell cultures themselves. After all, there is a theoretical possibility, which has been represented time and again by a minority [17], that cancer cells themselves contain infectious agents, such as bacteria or viruses. If this were so, then these particles would also be cultivated and isolated by means of the culture and nourishing procedures, along with the introduced inoculum.

It seems plausible to me that in the picture shown in this paper as figure 3, one particle is displayed which contains RNA, which has been measured, characterized and described in detail. However, whether this particle comes from the measles inoculum or from the cells themselves is not explicitly evident. The fact that this is not discussed as a problem may mean two things:

- There is a paper in which this has been done and which all other papers refer to. The papers already discussed above do certainly not fall into this category and a proof for this alleged possibility does not appear in any text.
- It has not yet been recognized as a methodological problem.

It seems to me that b) is the most likely scenario: if there was any awareness of a methodological problem, every author who publishes on the subject would feel compelled to quote the appropriate reference or would refer to it in a sentence in the method or discussion section. Since this does not happen, the problem was most likely not recognized, or if it was recognized, it was not deemed to be relevant.

Summarizing, this study may indeed have come up with a clear micrograph that can also definitely be addressed as virus particles. But both the mentioned polymorphism as well as the size variance, together with the already discussed lack of a systematic negative control in all studies seem to justify the doubt that the picture indeed shows a measles virus. Only a morphological analysis of the many shapes and an unambiguous characterization, e.g. through immunological methods and above all a powerful evidence that they *cannot be* structures originating and grown from the cell cultures, would dispel any doubts.

Publication no. 5

Horikami, S.M. & Moyer, S.A. (1995) Structure, transcription, and replication of measles virus. In: V. ter Meulen & M.A. Billeter (Eds) Measles Virus. Current Topics in Microbiology and Immunology 191 (pp. 35-50). Springer: New York, Heidelberg.

This publication summarizes approximately 120 other papers in a review and deals exclusively with the structure of the viral RNA, the gene coding and relevant studies on this subject. Thereby, this paper assumes that the issue of interest here has already been clarified and is *per se* irrelevant for the question discussed here. However, it shows that a very rich research network has been established by researchers, all of which obviously operate under the consensus that the viruses isolated here originated or are indeed derived from measles. The accuracy of this assumption is neither discussed nor challenged, but rather assumed, obviously. Thus, the factuality is confirmed. It is outside my competence to determine whether in the details of these analyses experts can find clear indications that the genome sequences or the behavior of RNA are typical for certain viruses or not. However, it is clear that this review does not contain any information on the method of isolation of the virus itself and on the methodological validity of this very first step. Rather, it is assumed as methodical matter of course. Whether this is the case can neither be determined on the basis of this publication nor of the previously discussed papers. From a formal perspective, it should perhaps be noted that even if Springer is a very good publishing house, such editorial compilations are subjected to a rather gentle review.

Publication no. 6

Daikoku, E., Morita, C., Kohno, T. & Sano, K. (2007) Analysis of morphology and infectivity of measles virus particles. Bulletin of the Osaka Medical College, 53 (2): 107-114.

This study analyzed the morphology and infectivity of the measles virus. At the beginning, the authors note that several other studies, including the one discussed above, had come to the conclusion that the infectious agent was polymorphic and had been observed in different sizes between 180-600 nm, or between 300 to 1000 nm, respectively. In addition, other studies had reported on the separation of the particles in three fractions. This is continued here. The authors used the Edmonston strain as well, without further information on how it was extracted. Different cells, among others simian cells, but also human cell lines were then infected with this strain. The cells are incubated and grown for seven days, after which infected cells are extracted via centrifugation and microfiltration. These are then examined by electron microscopy, both the conventional way and also with an immunological marker.

Just like in the other studies, polymorphic particles appear, which are defined as measles viruses. They have sizes between 50-950 nm. All particles in any size formation are infectious. Most particles have a size of 300 to 500 nm and are thus within the range of sizes observed by others. Particles can be marked with various immunological methods and show different fine structures when marked this way.

Methodological remarks and comments:

From a formal perspective, it should be noted that the "Bulletin of the Osaka Medical College" is a rather peripheral journal, which presently cannot even come up with an impact factor. Even some journals which publish mostly in German, like "*Der Schmerz*" (The Pain), "*Der Psychotherapeut*" (The Psychotherapist) or "*Forschende Komplementärmedizin*" (Research in complementary medicine) have impact factors, which shows that their papers are cited by other authors. The description of the journal on its own website suggests that no peer review takes place, but only an internal check. The journal is used mainly by members of the Osaka Medical College to communicate their findings. Thus, it is not a "high-ranking" paper, and one would have expected a ground-breaking result like the clear electron microscopy description to be published in a more popular journal.

The study rests, like all the others, upon the acceptability and validity of the extraction method. Therefore we have the same problem as with all the other studies: the extraction of the isolate follows the established pattern. It is presented here in an even shorter form: "MeV, the Edmonston strain, was inoculated ..." (p. 108). Through terms like "MeV" short for "measles virus" and "the Edmonston strain", the subject-specific research tradition is served.

We already saw in paper no. 3 the same choice of words and a reference to the original study by Enders & Peebles (1954), the latter being omitted here. One can therefore assume that, again, either a virus culture was carried out according to the method used by Enders & Peebles, or, more likely, that the infected cell line established by Enders & Peebles was used for the extraction of the isolate. However, this in turn means that everything that has happened or was omitted since that time happens or is omitted here as well. This may involve the introduction and further culture of another agent, or the further reproduction of substances or agents in the cell cultures. Since no systematic negative control was carried out, this cannot be established for sure. Despite the images and analyses being so compelling and the research tradition being so suggestive: it cannot be ruled out that what was isolated and presented here was an infectious agent of another nature or endogenous cell particles isolated from the measles culture. The short phrase "MeV, the Edmonston strain..." does not allow any decision on this matter. Control experiments are not mentioned.

In the final analysis, this study does not qualify to answer the present question either.

Discussion and conclusions

What do we learn from this situation? I am summarizing: none of the studies performs a really solid negative control to ensure that the potentially infectious agent is not already present in the starting material, in the monkey kidney cells or in the HeLa cells. Either the introduced agents themselves, or the agents interacting with the cell material, or the cell material itself, or all of this together with the isolate from the diseased tissue could be responsible for the observed changes.

In this context, it seems to me that the challenger, Dr. Lanka, is right: a single study cannot prove that there is a measles virus and least of all the studies submitted here.

Why, then, do we have the consensus in science and why does the science feel obviously distressed by such a troublemaker like Lanka who interferes with their business? This is obvious from Professor Podbielski's expertise, who points out that the picture results from the combined consideration of *all* findings, including the studies which are not the object of this trial.

Science has always been a cumulative social process. In the process of setting up the entire germ theory of diseases, the consensus developed that says measles must be an infectious process. Somehow, everyone expected that it should be possible to isolate something like a virus. Thus, the *a priori* expectation for a study to eventually lead to such a result was high. This is why all researchers condone the methodological weaknesses of the first studies, even if the authors themselves advise caution. Through the citation practice, factuality is suddenly generated, which subsequent negative studies - should there be such studies- can no longer easily revise.

This issue was recently proven in a very impressive way in a case in which a false theory had been supported for years, despite enough negative findings, for the simple reason that the most powerful authors supported the false theory and systematically suppressed negative findings. I am speaking of the theory that a certain form of myositis was caused by amyloid deposits. Only after many papers had been published and a lot of effort had been put into this, it came out that a) the theory was wrong, and b) this false opinion came into existence because facts had been created by citation networks. [18]

The longer it is passed on and the longer it is accepted by all, the more difficult it is to doubt this factuality. Yes, but: "there are all these genetic examinations, all these tests under the electron microscope", the proponents will say. Right. The question that Lanka has raised and which is entirely justified is as follows: has the *very first* data, on which all subsequent studies rely, actually been collected in a way that unequivocally proves that only the suspected causative agent was isolated? As we have seen, this is not the case. In the first studies - and none of the other submitted studies have eliminated this flaw - no negative controls were carried out. Thus, either the agents already existing in

the monkey cells or the famous “foamy agent” or agents caused by interaction or agents introduced with the additives or agents resulted from interaction with HeLa cells, or a mixture thereof could be responsible for the observed subsequent changes. Since all later methods and studies obviously rely on these first studies, the argument does not seem to have been refuted.

It could be dispelled by presenting a study which eliminates the problem. Either there is not such a study or the claimant has not found it and not submitted it.

This is an interesting situation. I'm curious to see how the court decides. Actually, in my view, this is what should happen right now:

A really good laboratory should carry out the isolation of the suspected measles virus from scratch and, by means of systematic negative controls, obtain an isolate which shows that the accompanying procedures - broth, infection, transfer into a cell strain - do not lead to infectivity and to the observed changes, and afterwards characterize the virus biochemically and by electron microscopy. This study would have to be previously registered and agreed upon in advance with a high-ranking journal, regardless of the outcome.

Or else, an expert researcher should come up with the paper in which this was done. The submitted papers do not do the job. It is more likely that everyone will go back to business as usual, because the questioning of a consensus which has lasted for almost half a century is quite high-priced.

Maybe the measles virus trial can give people a little food for thought. The discourse will be jogged properly only when a truly well-to-do virologist accepts this challenge. Perhaps Dr Lanka should take his money and call on a really good laboratory and initiate such a study? Maybe that would help. But again, I'm skeptical. After all, science is socially conditioned and subject to the same weaknesses as all other social interactions. And again: with enough chutzpah and persistence, the majority opinion can be challenged, if one is willing to take the beating which is to be expected initially. Whether thereafter a change occurs depends on two factors:

- whether one is actually correct and it turns out that the majority has been wrong until now, and
- if one manages to determine a reputable spokesman to speak out on this truth.

It will be thrilling. We are witnessing a historical lawsuit, in which the truth is on trial. Lanka pointed out with his challenge that the consensual truth is less certain than it seems. With his answer, Bardens tried to rise to the challenge. The studies presented, the analysis above shows it, are less powerful than one may think. By saying this, it is not questioned here that measles can be dangerous, that vaccines can possibly help etc., all that is not addressed here at all. The majority consensus is up for debate, the consensus that what has happened so far in science is sufficient to prove the measles virus as a fact. After everything I’ve seen up to now, this seems doubtful to me. Given the large replication problem in medicine [19] and the consequent risk of skepticism in the society, it would probably be wise if a few competent researchers set about dispelling these doubts through accurate replications, once and for all. Otherwise, just open the books anew. For the time being, it seems to me both versions are possible, but nothing is irrevocably proven.

Sources and Comments

[1] Advertisement for reward Klein-Klein-Verlag dated 24.11.2011

[2] Dean, K. (2004). The role of methods in maintaining orthodox beliefs in health research. Social Science and Medicine, 58, 675-685.

[3] *This debate has been very competently analysed by a scientific journalist. Even if not everything is accurately represented, the historical debate is of great importance: Teicholz, N. (2014). The Big Fat Surprise. Why Butter, Meat and Cheese Belong in a Healthy Diet. New York: Simon and Schuster. An example: the biggest randomised study ever on low-fat diets carried out with almost 50.000 women over 7 years shows that this dietary advice, considered to be the standard diet and scientifically proven for a long time, is completely useless both for weight loss and for heart attack prevention*: Beresford, S. A., Johnson, K. C., Ritenbaugh, C., Lasser, N. L., Snetselaar, L. G., Black, H. R., et al. (2006). Low-fat dietary pattern and risk of colorectal cancer: The women`s health initiative randomized controlled dietary modification trial. Journal of the American Medical Association, 295(6), 643-654. Howard, B. V., Manson, J. E., Stefanick, M. L., Beresford, S. A., Frank, G. R., Jones, B., et al. (2006). Low fat dietary pattern and weight change over 7 years: The Women's Health Initiative dietary modification trial. Journal of the American Medical Association, 295(1), 39-49. Howard, B. V., van Horn, L., Hsia, J., Manson, J. E., Stefanick, M. L., Wassertheil-Smoller, S., et al. (2006). Low fat dietary pattern and risk of cardiovascular disease: The Women's Health Initiative randomized controlled dietary modification trial. Journal of the American Medical Association, 295, 655-666.

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[9] Fleck, L. (1980). Entstehung und Entwicklung einer wissenschaftlichen Tatsache. Einführung in die Lehre vom Denkstil und Denkkollektiv. Mit einer Einleitung herausg. v. L. Schäfer und T. Schnelle. Frankfurt: Suhrkamp. (Original erschienen 1935).
Fleck, L. (1980). Genesis and development of a scientific fact. Introduction to the doctrine of thought style and thought collective. Frankfurt: Suhrkamp. (originally published in 1935)

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[11] *Stefan Baumgartner, who does research with potentised, serial highly diluted substances on plants, carries out his experiments in principle with systematic negative controls and the majority of researchers in this field do the same*. See Scherr, C., Simon, M., Spranger, J., & Baumgartner, S. (2009). Effects of potentised substances on growth rate of the water plant Lemna gibba L. Complementary Therapies in Medicine, 17, 63-70, oder Witt, C. M., Bluth, M., Albrecht, H., Weisshuhn, T. E. R., Baumgartner, S., & Willich, S. N. (2007). The in vitro evidence for an effect of high homeopathic potencies – A systematic review of the literature. Complementary Therapies in Medicine, 15, 128-138, *for an overview*.

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[13] However, Koch's postulates are now no longer sustained in their original form, because it has become clear that they are much too mechanistic. This very change in the historical context is extremely interesting, since it shows an implicit retraction from the mono-causal model, while –however- still trying to maintain this model in the general perception, by speaking of “pathogens”, “causative agent”, etc.

[14] *HeLa cells are culture cells derived from the tumour of Henrietta Lacks, who died in 1951; this cell line has been multiplied and can now be purchased.*

[15] This is the name of the boy from whom this first infectious material was obtained.

[16] Fleck, L. (1980). Entstehung und Entwicklung einer wissenschaftlichen Tatsache. Einführung in die Lehre vom Denkstil und Denkkollektiv. Mit einer Einleitung herausg. v. L. Schäfer und T. Schnelle. Frankfurt: Suhrkamp. (Original erschienen 1935). Genesis and development of a scientific fact. Introduction to the doctrine of thought style and thought collective. Frankfurt: Suhrkamp. (originally published in 1935)

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Kevles, D. J. (1997). Pursuing the unpopular: A history of courage, viruses, and cancer. In R. B. Silver (Ed.), *Hidden Histories of Science* (pp. 69-112). London: Granta Books. *Especially* the last text shows: each subsequent mainstream theory of cancer research was first fought as “outsider theory” before it was accepted.

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