History of glucocorticoid treatment of multiple sclerosis

Foreword

By analyzing the objective connections, the following essay questions the justifiability and meaningfulness of the current strategy for use of glucocorticoids in the context of the treatment of multiple sclerosis (MS for short). I believe that the existing therapeutic strategy is a paradigm in Kuhn's sense. I also believe that in this context Kuhn's statement that students accept "theories because of the authority of the teacher and the teaching book, not due to evidence",[1] becomes alarmingly real – In conclusion I shall demonstrate that a different use of glucocorticosteroids for the treatment of MS is at least conceivable and that this approach is worth testing empirically.

My findings in respect of the general investigation of glucocorticosteroids in the 1940s / 1950s are constantly expanding. This ultimately led to my writing another essay in 2015: „The observation of natural remissions in rheumatoid arthritis, the discovery of the effect of cortisone / cortisol and the dialectical conclusion from this for treatment of multiple sclerosis". I have since revised the 2014 essay and included in it large parts of my 2015 work. I hope thereby to make clearer the importance of the growth of knowledge from the early days of investigation of cortisol for therapeutic practice in general, and MS therapy in particular.

Formal aspects:

1. Since I intended from the outset to compose this work interactively, I have consistently referred to literature and articles which are freely available on the Internet, so that any reader can immediately access these without the need to visit the specialist medical university libraries. – In some places, especially in the presentation of the historical development of glucocorticosteroid treatment of MS, however, I have had to resort to written specialist books.
2. When referring to online scientific publications, I have used where possible the "Internet Archive" which archives digital data in freely accessible form as snapshots of web pages for long periods.[2]
3. The method of citation for internet publications follows the recommendation given by Florian Meixner on "historicum.net".[3] If a "snapshot" from the Internet archive is cited by me, I give its date after the URL. – For some internet publications, the form of citation is already predetermined by the publishers.
4. For the clarification of various issues I refer to Wikipedia articles. – Among German historians Wikipedia is not considered to be citable because the authors of the article are not mentioned by name. However, I believe that this does not greatly diminish the scientific quality of the articles and have therefore ignored such niceties within the scope of this essay.

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Contents

1. Introduction

Glucocorticoids / glucocorticosteroids have been used since the early 1970s as a drug in the treatment of individual symptoms of multiple sclerosis (MS for short) / encephalomyelitis disseminata (ED for short),[4] although they were first tested in September 1948,[5] and were available (or still are available) on the pharmaceutical market as “Hydrocortisone” from 1951 in the US and from 1953 / 54 in Europe.[6] This raises the question as to which MS treatment strategies with glucocorticosteroids were recommended at what point of time and why - as far as I have been able to answer this question in view of the availability of printed literature and internet sources.

Excursus *glucocorticoids / glucocorticosteroids*: It is fundamentally important to know that “Cortisone” is merely the colloquial generic term for active ingredients, similar in their chemical structure, but not identical.[7] “Glucocorticoids” is the generic term for all substances of this chemical category. A distinction is drawn between natural glucocorticoids occurring physiologically in the body, and synthetic glucocorticoids, which are used as drugs.[8] – Whether a glucocorticosteroid is a cortisone or rather a cortisol depends on whether a hydroxide (cortisol) or a keto group (cortisone) belongs to the molecule of the active ingredient;[9] for example: “Prednisolone” is a cortisol and not a cortisone.

Synthetic glucocorticoids used as pharmaceuticals are distinguished primarily by their potency. The so-called “Prednisolone equivalent” is used as a benchmark for determining potency. So for example 5 mg “Prednisolone” is roughly equivalent in strength to 4 mg “Methylprednisolone“ or 0.75 mg “Dexamethasone“.[10]

Natural glucocorticosteroids exert their effect in almost all cells of the organism and are practically ubiquitous, so for example they fulfil important functions in the metabolism of cells or affect the electrolyte balance. – Synthetic glucocorticoids are used because of their antiphlogistic and/or anti-inflammatory effect mainly for the inhibition of inflammations.[11]

The anti-inflammatory effect of glucocorticoids was discovered by the American rheumatologist Philip Showalter Hench. He had observed that pregnancy in patients suffering from rheumatism led to an interruption of the incidence of illness (he had also made this observation concerning persons with rheumatism who suffered from jaundice).

[12] All in all Hench observed this phenomenon systematically within the scope of studies in 1929, 1933, 1934, 1935, 1938 (in that year three times), 1940 and 1949. From this he inferred the working hypothesis that there must be a common biochemical cause for the coincidence of interruption of illness in rheumatism sufferers by pregnancy and jaundice, [13] and he suspected from 1938 that a hormone in the adrenal cortex might play a causative role here.[14]

Excursus *adrenal gland / adrenal medulla / adrenal cortex*: The adrenal glands are endocrine glands, arranged in pairs, each located on the upper pole of a kidney each. A single adrenal gland consists of the adrenal medulla, which primarily delivers adrenaline and noradrenaline to the blood, and the adrenal cortex, whose three layers secrete glucocorticoids, mineralocorticoids and sex hormones into the bloodstream.[15]

What inspired Hench‘s presumption that there could be a biochemical cause for rheumatoid arthritis? – In 1905 the term „hormone“ as a category for such substances as “insulin” (http://flexikon.doccheck.com/de/Insulin) was established by the British physician Ernest Starling. Starling had here the idea of a “body regulated by chemical messengers” (today we know that this category consists of very diverse chemical substances).[16] – Anyway, in the decades after 1900, various hormones and the interrelationships with diseases caused by a shortage of them were discovered. Against this historical background, patients with Addison’s disease have been treated successfully since the early 1930s with an extract from the adrenal cortex of animals for slaughter known as “Cortin”.[17]

Excursus *Addison’s disease (Addison’s melanoderma)*: as a result of impairment to the adrenal cortex (cortex glandulae suprarenalis), which produces inter alia steroid hormones, of which cortisol is one, the body reaches a state of cortisol insufficiency. – up to the end of the 1920s, Morbus Addison led sooner or later to the death of the Addison’s sufferer because the missing hormones are vitally important for the body’s metabolism.[18]

From this it was clear that physiologically active hormones must be present in this extract. Work on isolating these hormones was carried out by the chemists Tadeusz Reichstein (Switzerland) and Edward C. Kendall (USA),[19] the latter worked, like Hench, at the Mayo Clinic in Rochester.

Reichstein and Kendall succeeded at roughly the same time in 1937 in isolating the hormone cortisol (17-Oxy-11-dehydro-corticosterone)[20], which was named “Compound E” by Kendall and “Substance Fa” by Reichstein.[21] Reichstein was, however, the first (1943) to manage to synthesise the hormone from ox gall (Kendall could extract the hormone only from existing adrenal cortices).[22]

In connection with the expected entry of the USA into the Second World War , investigation of adrenal hormones by the “Mayo-Clinic“ was encouraged by the US government from 1941. The aim was to develop a doping agent for fighter pilots that would prevent them from fainting at high altitude.[23] It should be mentioned that there were no mass-produced pressurised cabins or pressure suits for pilots available anywhere in the world in 1941/42. [24] In addition it was assumed that the enemy power – Germany – would also push on

with the investigation of these hormones for the very same reason.[25] – The involvement in the research process of chemists from the firm of “Merck” from 1942 must also be seen in this context.[26] Here it was a question of preparation for the industrial mass production of a drug which might be strategically important. – The medical importance of Compound E, however, was not recognized until 1948 in a trial conducted by the rheumatologist Hench at the “Mayo Clinic“.

2. The discovery of the effect of cortisol in rheumatoid arthritis

As previously shown, from 1938 Hench thought it likely that one of the adrenocortical hormones was responsible for the remissions observed in rheumatoid arthritis.[27] – In January 1941 Hench und Kendall decided at an internal conference in the Mayo Clinic to test Compound E on patients suffering from rheumatism, as soon as it was available in sufficient quantity for medical research,[28] and in September 1948 sufficient amounts of the hormone were finally available, synthesized by the American pharmaceutical company Merck.[29]

Compound E was first injected on September 21, 1948 to a young woman suffering from severe rheumatism at a dose of 100 mg; up to September 28 further daily injections were made of 100 mg of this substance. Thereafter the dose was reduced for four days to 50 mg, then again to 25 mg per day for 10 consecutive days. – The reduction of the dose however turned out according to Hench to be a mistake, because the “erythrocyte sedimentation rate” fell from 111 to 86 mm from the start of treatment and then rose rapidly, finally reaching 118 mm.[30]

Excursus *erythrocyte sedimentation rate*: The erythrocyte sedimentation rate (ESR for short) is a non-specific laboratory test to determine whether there are inflammations in the body, because where inflammations are present the red blood cells (erythrocytes) will sink faster in a 3.8 % sodium citrate solution in a specially graduated glass tube than with healthy persons. – Erythrocytes normally have a negative surface potential and repel each other. In an inflammation process however this surface potential is reduced, resulting in the formation of cell aggregates (so-called “rolls of coins“). Cell aggregates are heavier than individual erythrocytes and therefore sink faster.[31]

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3. Etiology and pathogenesis of rheumatoid arthritis, and determining the initial dose of Compound E in the year 1948. – Etiology and pathogenesis of disseminated encephalomyelitis (encephalomyelitis disseminata).

Hench‘s assumption that there might be a biochemical cause for rheumatoid arthritis[32] is remarkable insofar as this disease is nowadays considered an autoimmune disease of unknown etiology (we now also know that among other characteristics glucocorticoids develop an immunosuppressive effect)[33].

Excursus *rheumatoid arthritis / primary chronic polyarthritis*: The etiology is largely unexplained, but it is known that antigenes are released in the conjunctive tissue, and in turn activate the formation of antibodies by the immune system. This results in the formation of anti-antibodies, which form so called immune complexes with complement,

antigenes and antibodies. These immune complexes are admittedly deposited in the conjunctive tissue of the entire body, but in the early stage of the disease there are usually inflammation reactions in the joints first of all, and in time these eliminate the immune complexes.[34]

When Hench, however, came up with the idea of trying out the newly discovered adrenocorticosteroids individually but unsystematically for the treatment of rheumatoid arthritis (although there were also setbacks)[35] so-called "modern immunology" was still in its infancy.[36] He therefore had only a vague idea of the etiology of this disease and no idea of its pathogenesis! Hench‘s experiments were thus based solely on systematic observation of patients, without knowing the effect of Compound E at a cell level; nor had he or Kendall previously determined the body-specific reference values for this hormone.

Excursus *Etiology and pathogenesis of multiple sclerosis*: Multiple sclerosis is also regarded as an autoimmune disease.[37] It is thought to be triggered by T-lymphocytes, which mistakenly confuse the surface of the myelin with the antigens of pathogens.[38] It is extremely important here to understand that the T-cells do not belong to the central nervous system (CNS for short) but to the immune system of the rest of the body where they do not cause any harm. Only the fact that they can cross the blood-brain-barrier makes them dangerous (according to the model).[39] – For this reason, immuno-suppressants also have such devastating side effects, because they already damp the immune response / the T-lymphocytes on this side of the blood-brain-barrier, where they are urgently needed for defence against infection and tumor!

According to auto-immune theory, T-lymphocytes are ‘trained’ to cross vessel barriers on their way through the lung in the course of blood circulation before the disease actually breaks out.[40] Having arrived in the CNS, the T-cells are supposed to identify the myelin as extraneous to the body and differentiate themselves into their different subgroups. These include cytotoxic T-lymphocytes, which can directly attack oligodendrocytes and neurons. Another subgroup of the T-cells, type-1 T-helper cells emit cytokines that could damage the blood-brain-barrier and thus enable other cells of the body’s immune system to enter the CNS.[41]

In view of the lack of concrete ideas about the pathogenesis of rheumatoid arthritis, the question arises as to the scientific basis on which the initial dose of 100 mg Compound E for the first therapy experiment was actually determined by the chemist Kendall (not by rheumatologist Hench).[42]

The doctor and former companion of Hench – John Glyn – comments on this question in an essay from December 1997: “No one has ever explained to me why they decided to use the pharmacological dosage of 100mg for initial injections. This corresponds to at least ten times the dose of DOCA then recommended for treatment of Addison's disease. Had they used the smaller dose, the anti-inflammatory potential of corticosteroids might have taken much longer to emerge, Merck might have abandoned the costly quest for commercial synthesis and the progress of corticosteroid research might have been much delayed. They were also lucky in the size of the crystals which they used. Had the crystals been larger they would probably have formed depots at the injection sites, with inadequate absorption (to say nothing of the fact that depot residues of injected steroids can cause horrific abscesses)”.[43]

Glyn is right in his conjecture that Merck was on the verge of shelving investigation of Compound E for want of proof of usefulness; because even during the war it became clear that Compound E (at a relatively low dosage) was unsuitable as a doping agent for short-term performance, and no medicinal benefit could be identified either (unfortunately, Rook does not support this assertion with a source).[44] – Furthermore Glyn's statement must be qualified insofar as DOCA (deoxycortone acetate) is not a glucocorticoid, but the acetate form of the mineralocorticoid "21-hydroxy-4-pregnene-3.20-dione"; the comparability of the dosage of these substances is therefore not directly given.[45]

More important than the comparison with DOCA is the fact that in 1946, there had already been trials of the chemically closely-related substance "Compound A" at the Mayo Clinic. These trials had been conducted by the rheumatologist Dr. Edwin Kepler and he had chosen a dose of 200 mg for this purpose.[46] There was therefore already a model for Kendall to use in determining the initial dose of Compound E. Furthermore, according to Rook, experiments with 50 mg of Compound E had already been carried out without success,[47] although it is unclear to which trials he is referring here.

4. History of the glucocorticoid treatment of multiple sclerosis

The question whether glucocorticoids have a positive effect on MS relapses was investigated very early, with the conclusion that they were ineffective. The physician J. M. Carlisle published an article to this effect in the "British Medical Journal" in 1950, describing the possible areas of application of glucocorticosteroid treatment.[48]

Excursus *James M. Carlisle*: Carlisle was the medical director of the American pharmaceutical company Merck. He met Hench for the first time a week after the first successful trial of Compound E in New York. On behalf of Merck, Carlisle was to verify the apparently pioneering results of research at the Mayo Clinic in the following weeks, or decide whether the pharmaceutical company would pull out of the project.[49]

In the very same year 1966 Klaus Poek wrote in his textbook "Introduction to clinical neurology" about the treatment of multiple sclerosis: "Great hopes had been attached to treatment with adrenal cortex preparations. Since then, statistical studies at many hospitals have shown that improvement does not come after corticosteroids more frequently or more rapidly than was expected after the initial prognosis."[50]

It was not until 1969 that a study on MS treatment with glucocorticoids produced results that were opposed to those of Carlisle.[51] – Consequently Poek also began in 1972 a tentative revision of his recommendations on treatment in the second edition of his book: „Adrenal cortical preparations [highlighted in the original] have no effect, even according to the latest statistics (double blind test). Only in acute life-threatening conditions, such as fresh sites in the medulla oblongata, can prednisone be given for a short time at a daily dose of 100 mg under the protection of antacids, in order to possibly bring about a change for the better. Corticoid treatment is absolutely indicated in optic neuritis, whatever the etiology. "[52]

No later than 1978, in the fifth edition of his book (the intervening editions were not available to me for evaluation), Poek definitively abandons his restriction made in 1972 of the use of glucocorticosteroids to optic neuritis and MS foci in the medulla oblongata. He

recommends logically the administration of an initial dose of 100 mg Decortilen in principle, which is then "tapered" over several weeks.[53]

In the eighth edition of his book, published in 1992, Poek hesitantly begins to withdraw from the initial recommended dose of 100 mg methylprednisolone by equating its effectiveness with a so-called "pulse therapy" of 500 mg over 5 days.[54]

Excursion *Potency of various glucocorticoid preparations*:[55]

Trade Name **(Note: German trade names!)**	**Active ingredient**	**Potency** **(Cortisol = 1)**
e.g.: Decortin®	Prednisone	4
Decortilen®	Prednylidene	4
e.g.: Urbason®	Methylprednisolone	5

In 1998, Poek finally abandons his original recommendation for dosage regimens definitely without comment and recommends only the pulse therapy with 500 mg methylprednisolone over 5 days or 1.000 mg over 3 days.[56] – In 2006, in the 12th edition of the textbook co-edited by Werner Hacke, there is even an explicit warning against the original recommended dose: "Initial doses of 100 mg per day have no better effect on relapses than placebo."[57])

The guidelines of the "Deutsche Gesellschaft für Neurologie” (German Society of Neurology" (DGN for short) from the year 2008 accordingly also recommend the pulse therapy over 5 or 3 days and then a repetition of the pulse therapy with twice the quantity of Methylprednisolon, if the symptoms have not improved 14 days after the end of the first pulse therapy.[58]

5. Conclusion

From the very beginning, the unspoken question as to the correct dosage of synthesised cortisol loomed. - Hench made the fundamental mistake of refraining from the deeper

investigation of the natural processes after the successful attempt in 1948, and instead, of using false premises as a basis for drawing conclusions for medical practice!

His approach to treatment was based on the combination of practical observation of patients over many years and an over-simplified theory about hormonal control of bodily processes by hormones of the adrenal cortex; but Hench's and Kendall's actual error was that, after the trial which identified compound E (cortisol) as the crucial hormone, they did not investigate at what natural concentration it occurs in the body of women (with rheumatism) during pregnancy! - In fact, the reference values for maternal blood cortisol bound and unbound to blood proteins rise ‘sharply’ in healthy women during normal pregnancy, but these values are in the range of micrograms![59] In order to understand the actual meaning of these facts, one must realise that one microgram (µg) is one-millionth of a gram, and one milligram (mg) is one-thousandth of a gram;[60] so a microgram is one-thousandth of a milligram. - An almost homoeopathic concentration!

Excursus *Microanalysis*: From 1910, the Austrian chemist Fritz Pregl established the principles of quantitative analysis of the chemical composition of organic material[61] "in the smallest sample quantities, as are generally available for clinical chemical investigations",[62] and "allowed or accelerated the structural elucidation of many biologically important natural products such as vitamins and hormones."[63]

Pregl published his groundbreaking research results in the monograph "Die quantitative organische Mikroanalyse”(Quantitative organic microanalysis) (1917, 3rd edition, 1930).[64] - In 1923 he was awarded the Nobel Prize for Chemistry for the development of microanalysis.[65]

As shown by the above excursus on microanalysis, Kendall and Reichstein could have known about the natural concentration of cortisol, since quantitative chemical analysis of organic matter had been widely used since at least 1923.[66] In fact, neither Kendall nor Reichstein carried out quantitative analyses, but confined themselves to purely qualitative analysis of the chemical components of the adrenal cortex and the synthetic manufacture of cortisol. For his trials Hench therefore had no reference points based on the analysis of natural concentrations for the dosage of Compound E.

Instead, he attempted to continuously lower the drug dose from a high level, with the effect that the inflammation processes intensified again; Hench again drew the (wrong) conclusion that 100 mg Compound E was the optimal dose. In fact, his investigations only prove that the human organism does not tolerate this approach (gradual lowering of a high initial dose)! Apart from this, the initial dose for the experiment of 1948 had been deliberately set very high in order to achieve short-term success in treatment, since the potential producer (Merck) had still to be convinced of the synthetic production of the substance on an industrial scale.

In addition, the investigations were made without exception in severe cases of rheumatism[67], whereas it is unclear at which stage of rheumatism (there are four in total) the women were on whom he performed his observations. Hench's final generalization of the dosage for all rheumatism patients is therefore absolutely arbitrary, since many parameters were simply unclear and / or not yet defined (e.g. the identification of stages of rheumatism by Steinbrocker et al. dates from 1949)[68]!

Carlisle - and after him, all conventional medicine - adopted Hench’s / Kendall's

determination of the therapeutically effective dose not only without evaluation for Compound E, but this determination was essentially maintained also for other, more powerful glucocorticoids up to the present day, and generalised for all chronic diseases across the board. This is also true for multiple sclerosis (the same phenomenon is also observed in pregnant multiple-sclerosis patients in the second and third trimester, as in pregnant rheumatics)[69].

An examination of the historical development of possible and then actual glucocorticoid use in the treatment of multiple sclerosis underscores this causal nexus: It is striking that initially (following Carlisle's lead) the effectiveness of this drug in relation to multiple sclerosis was disputed for at least 16 years (1950 to 1966). Thereafter, a continuous increase in doses and an increase in the strength of the glucocorticosteroids used, took place in the period from 1972 to 1998. - So in 1972 Poek recommended 100 mg "Prednisone", whereas in 1978 it was 100 mg "Decortilene" in 1978 and in 1992 100 mg "Methylprednisolone".

It is also interesting that in 1972 Poek limited the use of Prednisone to the treatment of inflammation sites in the medulla oblongata and opticus neuritis. The effect of corticosteroids in these areas of the CNS seems to him to be self-evident. He fails to explain why an effect in the thalamus for example, which is just as much a component of the CNS, is less likely or even unlikely.

The development towards ever higher doses of ever more potent glucocorticoids culminates in Poek's and Hackes' claim in 2006 that the administration of 100 mg methylprednisolone is equivalent to a placebo effect. - It should be noted that the old recommended dosage was verified by the time-honoured method of the double blind study. This again raises the question whether the physicians were working negligently at the beginning of the 1970s or whether the method of the double blind study as such is unsuitable in determining a correct recommended dosage!

The misconceptions of scientists in the early phase of cortisol research are based on an unfortunate concatenation of circumstances. The real scandal however is that the physiological concentrations are now well researched, but so far no conclusions have been drawn from them about the dosage and use of synthetic glucocorticoids!

The difficulty in determining the correct glucocorticoid dose for the treatment of multiple sclerosis is due to the nature of the matter itself, since –to put it trivially - one cannot cut open the head of a (living) MS patient and watch 'how the drug works' at the cell level in the central nervous system of the patient. For this very reason the investigation of MS pathogenesis is not possible!

For multiple sclerosis, which is thought of as "rheumatism of the nervous system"[70], an autoimmune pathogenesis is assumed, in which the T4-lymphocytes play a decisive role.[71] But nearly all our (supposed) knowledge about the autoimmune disease processes of multiple sclerosis is based on the unobservable MS pathogenesis of the animal model, "experimental autoimmune encephalomyelitis" (EAE for short). Although it is true that by means of dissection and histological examination of the CNS of dead MS patients T4-lymphocytes can be found in the disease sites, it has been known for some years that 'normal' immune cells also migrate into the brain of stroke patients[72], and no one would think of reinterpreting stroke as an autoimmune disease!

Excursus on the investigation of MS by *experimental autoimmune encephalomyelitis* (EAE for short): The animal model, the so - called EAE, is crucial to the view of multiple

sclerosis as autoimmune disease,[73] because it allows the observation of the (supposed) pathogenesis of MS at a cell level under the microscope. For this purpose, the diseased laboratory animals are killed after a given time, and their CNS is histologically examined. This approach is, of course, not possible in humans.

However, because animals do not suffer from multiple sclerosis, they are injected with proteins of the myelin sheaths surrounding the nerve fibres. In fact, however, "Freund's adjuvant" must be added to the myelin proteins to trigger an EAE with as many test animals as possible. The so-called "Freund's complete adjuvant" (FCA for short) consists of mineral oil, inactivated tubercle bacilli and an emulsifier.[74]

For the time being, the EAE cannot be replaced, because modern imaging techniques, such as magnetic resonance imaging (MRI for short)[75] are not suitable for imaging at the cell level, the level of the immune system or for observing the disease and the effect of drugs on the immune cells in the CNS of the living patient. Nevertheless, it is possible to visualize the decay of the inflammatory process with the aid of certain contrast tools in the MRI.[76] - Although there are two other animal models of MS, all three models are more similar to each other than to human multiple sclerosis.[77]

Ultimately, quite a lot is known about the pathogenesis of animal EAE, but rather little about that of human MS!

Therefore the objective truth in the case of multiple sclerosis is that no one, not even a so-called expert, knows what this disease actually is, because at the cell level in humans only its consequences can be observed (once the MS patient is dead) but not the disease process itself! It should also be noted that the symptoms of multiple sclerosis are merely a consequence of the inflammation processes in the CNS and not multiple sclerosis itself. This means that glucocorticosteroid preparations could in principle have stopped the inflammation itself without any of the symptoms having improved, as the subsidence of the symptoms is accompanied by the regeneration capacity of the myelin sheaths, the so-called "remyelination".[78] Where the myelin sheaths are completely demyelinated regeneration will not take place anymore![79] – from this it follows that the results of a double blind study on the efficacy and recommended dosage of corticosteroid treatment in multiple sclerosis are critically dependent on whether the participants are already in an advanced stage of MS with more or less completely demyelinated plaques!

As has already been shown in the excursus on rheumatoid arthritis, it too is regarded as an autoimmune disease. - Interestingly, however, Hench himself (at least at first) had no idea of the autoimmune disease process of rheumatoid arthritis, since research on immunology in the modern sense had only begun in the 1930s. Even then however, Hench succeeded in "inventing" an effective treatment for this disease, solely on the basis of patient observations, without having had any idea of a disease in the sense of Virchow's cellular pathology!

By observing the course of the disease in pregnant MS-patients, it can be concluded that this is analogous to the course of disease in pregnant rheumatism patients. An adequate dialectical conclusion would therefore be that the remission due to pregnancy in both diseases is due to the same immediate cause, namely a minimally elevated cortisol level in the blood of the pregnant woman! – The answer to the question whether glucocorticoids in multiple sclerosis primarily affect the immune system of patients or become effective in some other form (we know that they perform a multitude of tasks in the organism at the cell level)[80]), is unimportant for successful treatment!

For the treatment of rheumatoid arthritis, a medical study was conducted in 2000 which showed that even with a dose of 5 mg Prednisolone (equivalent to approximately 25 mg compound E)[81] good results can be achieved (this form of treatment is known as "Low Dose Prednisolone Therapy", (LDPT for short).[82] The German neurologist Dr. Weihe, however, declares himself against LDPT in multiple sclerosis, as no long-term positive influence on the course of the disease is proven, and indeed long-term intake of cortisone at this dosage is associated with severe side effects (cortisone osteoporosis).[83]

The principal reason for the error in reasoning of conventional medicine in relation to LDPT is in determining the dosage of Prednisolone at 5 mg, because if you visualise the natural concentration of cortisol in the blood of pregnant women, this suggests that this dosage too has been fixed arbitrarily! - However, the study points in the right direction because it proves that with a dose which leads to a further increase in inflammation levels according to Hench, treatment can very well succeed, and the research should lead to further studies with even lower doses or weaker cortisone preparations!

Summary of the core theses of this conclusion:

1. Glucocorticoids have been administered from the very beginning in scientifically unjustifiable dosages. - The level of these dosages was passed on unthinkingly from one generation of medics to the next; this applies to glucocorticoid treatment in general, and to treatment of rheumatoid arthritis and of multiple sclerosis in particular.
2. Both dosage and duration of treatment must be based on the pattern of natural remission in rheumatism and MS. In practice this means the administration of very small amounts over long periods of time.
3. In connection with the possible significance of the initial dose for the effect of glucocorticoid treatment, pulse treatment has to be redefined. This means that in the case of pulse treatment, a 'surprise effect' may play a more important role for the body than the amount of glucocorticosteroids administered.
4. Medicine must free itself from its fixation on the regression of symptoms as a standard for glucocorticoid treatment and replace it with the reduction of the rate of attacks or the decrease of lesions, which become visible with MRI images.
5. Furthermore medicine must abandon its fixation on the clarification of the etiology and pathogenesis in the case of multiple sclerosis because, for the reasons given, it can currently only be investigated by means of an absurd animal model. - The exploration of the animal model for multiple sclerosis is parascience; the development of drugs based on this animal model for MS is paramedicine!

6. References

[1] Kuhn, Thomas S. [German translation Vetter, Hermann]: Die Struktur wissenschaftlicher Revolutionen (The structure of scientific revolutions), 2nd revised edition, Frankfurt am Main 1976, p. 93.

[2] No author information: Internet Archive, in: Wikipedia, URL: http://web.archive.org/web/20160515145659/https://de.wikipedia.org/wiki/Internet_Archive (15.05.2016)

[3] Meixner, Florian: Scientific publications on the web, in: historicum.net, URL: https://www.historicum.net/themen/reformation/reformation-digital/reformation-im-

www/institutionelle-und-wissenschaftliche-inhalte/wissenschaftliche-publikationen-im-netz/ (25.05.2016)

[4] Poek, Klaus: Neurology – Ein Lehrbuch für Studierende und Ärzte (A textbook for students and doctors), 2nd edition, Berlin / Heidelberg / New York 1972, p. 344.

[5] THE EFFECT OF A HORMONE OF THE ADRENAL CORTEX (17-HYDROXY-11-DEHYDROCORTICOSTERONE: COMPOUND E) AND OF PITUITARY ADRENOCORTICOTROPHIC HORMONE ON RHEUMATOID ARTHRITIS* – PRELIMINARY REPORT BY: PHILIP S. HENCH, EDWARD C. KENDALL, CHARLES H. SLOCUMB, and HOWARD F. POLLEY - From the Mayo Clinic, Rochester, Minnesota, U.S.A. – Ann Rheum Dis. 1949 Jun; 8(2): p. 98.

[6] Klinkenberg, Norbert: CORTISON – DIE GESCHICHTE DES CORTISONS UND DER KORTIKOSTEROIDTHERAPIE – EIN BEITRAG ZUR FORSCHUNGS- UND THERAPIEGESCHICHTE HEUTIGER MEDIZIN (THE HISTORY OF CORTISON AND CORTICOSTEROID TREATMENT - A CONTRIBUTION TO THE RESEARCH AND TREATMENT HISTORY OF TODAY'S MEDICINE), Köln/Cologne 1987, p. 88.

[7]
a) No author information: Cortison, in: Wikipedia, URL: http://web.archive.org/web/20160421222150/https://de.wikipedia.org/wiki/Cortison (21.04.2016)
b) Without author: Cortisol, in: Wikipedia, URL: http://web.archive.org/web/20160430111925/https://de.wikipedia.org/wiki/Cortisol (30.04.2016)

[8] Antwerpes, Frank / Offierowski, Nina / Weber, Bettina: Glucocorticoid, in: DocCheck Flexikon, URL: http://web.archive.org/web/20160315091901/http://flexikon.doccheck.com/de/Glukokortikoid?utm_source=www.doccheck.com&utm_medium=web&utm_campaign=DC%2BSearch (15.03.2016)

[9]
a) Bender, Sabine: DIE PTA IN DER APOTHEKE (THE PTA* [*pharmaceutical technician, female] IN THE PHARMACY), October 2015, p. 93.
b) No author information: Cortison, in Lexikon der Biochemie (in Dictionary of Biochemistry): http://www.spektrum.de/lexikon/biochemie/cortison/1400 (25.03.2016)

[10] Langer, H. E.: Prednisolon-Äquivalent (Prednisolone Equivalent), in: rheuma-online, URL: http://web.archive.org/web/20140709012658/http://www.rheuma-online.de/a-z/p/prednisolon-aequivalent.html (09.07.2014)

[11] Antwerpes, Frank / Offierowski, Nina / Weber, Bettina: Glukokortikoid (Glucocorticoid), in: DocCheck Flexikon, URL: http://web.archive.org/web/20160315091901/http://flexikon.doccheck.com/de/Glukokortikoid?utm_source=www.doccheck.com&utm_medium=web&utm_campaign=DC%2BSearch (15.03.2016)

[12] Kohl, Franz: Cortison, die Wunderdroge gegen Rheuma (Cortisone, the miracle drug for rheumatism), Eschborn 2001, in: kraniopharyngeom.de, URL: http://web.archive.org/web/20160311182326/http://kraniopharyngeom.de/infos/texte/cortison.htm (11.03.2016)

[13] THE EFFECT OF A HORMONE OF THE ADRENAL CORTEX (17-HYDROXY-11-DEHYDROCORTICOSTERONE: COMPOUND E) AND OF PITUITARY

ADRENOCORTICOTROPHIC HORMONE ON RHEUMATOID ARTHRITIS* – PRELIMINARY REPORT BY: PHILIP S. HENCH, EDWARD C. KENDALL, CHARLES H. SLOCUMB, and HOWARD F. POLLEY - From the Mayo Clinic, Rochester, Minnesota, U.S.A. – Ann Rheum Dis. 1949 Jun; 8(2): p. 97.

[14] Kaiser, Hans / Klinkenberg, Norbert: CORTISON – Die Geschichte eines Medikamentes (The history of a drug), Darmstadt 1988, pp. 50 and 52.

[15]
a) Nebenniere (adrenal gland). In: Pschyrembel – Klinisches Wörterbuch (Clinical Dictionary), 257th Edition, 1994 Berlin / Boston, pp. 1040 – 1042.
b) Antwerpes, Frank / Krieger, Tim / Sennholz, Hanno: Nebenniere (adrenal gland), in: DocCheck Flexikon, URL: http://web.archive.org/web/20160402035204/http://flexikon.doccheck.com/de/Nebenniere (02.04.2016)

[16]
a) No author information: Hormone (hormones), in: Wikipedia, URL: http://web.archive.org/web/20160422045158/https://de.wikipedia.org/wiki/Hormon#Definition (22.04.2016)
b) Haller, Lea: Cortison – Geschichte eines Hormons (The story of a hormone), 1900 – 1955, Zürich (Zurich) 2012, pp. 25, 31 and 40 – 41.

[17] Haller: 2012, p. 76.

[18] Addison-Krankheit (Addison's disease). In: Pschyrembel – Klinisches Wörterbuch (Clinical Dictionary), 266th Edition 2014 Berlin / Boston, pp. 22 – 23.

[19] Haller: 2012, p.76.

[20] Kaufmann, Hans P.: Arzneimittel-Synthese (pharmaceutical synthesis) – Eine neuzeitliche Darstellung dieses für den Chemiker, Apotheker, Arzt und die pharmazeutische Industrie wichtigen Forschungsgebietes (A modern account of this field of research, which is important for the chemist, pharmacist, physician, and the pharmaceutical industry), vol. 1, Heidelberg 1953, p. 499. vol. 1, Heidelberg 1953, p. 499.

[21] Haller: 2012, p. 105.

[22] Rook, Thom W.: The quest for cortisone, Michigan 2012, pp. 117, 131.

[23] Kendall, Edward C.: Cortisone, New York 1971, p. 99.

[24]
a) No author information: Druckkabine (pressurized cabin), in: Wikipedia, URL: http://web.archive.org/web/20160515145833/https://de.wikipedia.org/wiki/Druckkabine#Geschichte
b) No author information: Druckanzug (pressurized suit) / Piloten-Höhenschutzanzug (height protection suit for pilots), in: Wikipedia, URL: http://web.archive.org/web/20150908203012/https://de.wikipedia.org/wiki/Druckanzug#Piloten-H.C3.B6henschutzanzug (08.09.2015)

[25] Kendall, Edward C.: Cortisone, New York 1971, p. 99.

[26] ibid., pp. 121 to 122.

[27] Klinkenberg, Norbert: CORTISON – DIE GESCHICHTE DES CORTISONS UND DER KORTIKOSTEROIDTHERAPIE – EIN BEITRAG ZUR FORSCHUNGS- UND THERAPIEGESCHICHTE HEUTIGER MEDIZIN (THE HISTORY OF CORTISONE AND

CORTICOSTEROID TREATMENT - A CONTRIBUTION TO THE RESEARCH AND TREATMENT HISTORY OF TODAY'S MEDICINE), 1987 Köln, pp. 70 – 71.

[28]
a) Philip S. Hench: The Reversibility of Certain Rheumatic and Non-rheumatic Conditions by the Use of Cortisone or of the Pituitary Adrenocorticotropic Hormone. Nobel Lecture, December 11, 1950, in: The Nobel Foundation (ed.): Nobel Lectures, Physiology or Medicine 1942 – 1962. Amsterdam 1964 [1950], p. 318.
b) Hench / Kendall / Slocumb / Polley: Ann Rheum Dis. 1949 Jun; 8(2): p. 98.

[29] Rook: 2012, pp. 129 -130.

[30] Hench / Kendall / Slocumb / Polley: Ann Rheum Dis. 1949 Jun; 8(2): p. 99.

[31]
a) No author information: Blutsenkungsreaktion (ESR), in: Wikipedia, URL: http://web.archive.org/web/20160311083842/https://de.wikipedia.org/wiki/Blutsenkungsreaktion (11.03.2016)
b) Blutkörperchensenkungsgeschwindigkeit (erythroctye sedimentation rate). In: Pschyrembel: 2014

[32] Hench / Kendall / Slocumb / Polley: Ann Rheum Dis. 1949 Jun; 8(2): p. 97

[33] Glukokortikoide (glucocorticoids). In: Pschyrembel: 2014, pp. 798 – 799.

[34] rheumatoide Arthritis (rheumatoid arthritis). In: Pschyrembel: 2014, pp. 172 – 174.

[35] Kaiser, Hans / Klinkenberg, Norbert: 1988, pp. 51 – 52.

[36] No author information: Immunologie (immunology), in: Wikipedia, URL: http://web.archive.org/web/20160424221103/https://de.wikipedia.org/wiki/Immunologie#Beginn_immunologischer_Forschung (24.04.2016)

[37] No author information: Multiple Sklerose (multiple sclerosis) - (MS): Ursachen (causes), in: onmeda.de, URL: http://web.archive.org/web/20160412092708/http://www.onmeda.de/krankheiten/multiple_sklerose-ursachen-1471-3.html (12.04.2016)

[38]
a) Witte, Felicitas: Multiple Sklerose (multiple sclerosis) – Immunsystem (immune system), in: netdoktor.de, URL: http://web.archive.org/web/20091003083335/http://www.netdoktor.de/Krankheiten/Multiple-Sclerosis/Wissen/Multiple-Sklerose-Immunsystem-9931.html (03.10.2009)
b)
Bellmann-Strobl, Judith: Läsionsentwicklung in der Multiplen Sklerose: eine prospektive klinische und kernspintomographische Verlaufsuntersuchung, (Lesion development in multiple sclerosis: a prospective clinical and nuclear spinal tomography follow-up study), Berlin 2010, p. 12.

[39] Ulrich, Oliver: DAS IMMUNSYSTEM DES ZNS - MOLEKULARE MECHANISMEN DER BALANCE ZWISCHEN SCHUTZ UND SCHÄDIGUNG, in: MAGDEBURGER WISSENSCHAFTSJOURNAL (THE IMMUNE SYSTEM OF THE CNS - MOLECULAR MECHANISMS OF THE BALANCE BETWEEN PROTECTION AND INJURY, in: SCIENCE JOURNAL OF MAGDEBURG), 1-2/2005, p. 3.

[40] Odoardi, Francesca / Sie, Christopher / Streyl, Kristina / Ulaganathan, Vijay K. / Schläger, Christian / Lodygin, Dimitri / Heckelsmiller, Klaus / Nietfeld, Wilfried / Ellwart,

Joachim / Klinkert, Wolfgang E. F. / Lottaz, Claudio / Nosov, Mikhail / Brinkmann, Volker / Spang, Rainer / Lehrach, Hans / Vingron, Martin / Weckerle, Helmut / Flügel-Koch, Cassandra / Flügel, Alexander: T cells become licensed in the lung to enter the central nervous system, in: nature.com, URL: http://web.archive.org/web/20151031104604/http://www.nature.com/nature/journal/v488/n7413/full/nature11337.html (31.10.2015)

[41] Bellmann-Strobl, Judith: Läsionsentwicklung in der Multiplen Sklerose: eine prospektive klinische und kernspintomographische Verlaufsuntersuchung (Lesion development in multiple sclerosis: a prospective clinical and nuclear spinal tomography follow-up study), Berlin 2010, p. 12.

[42] Rook: 2012, pp. 140 -141.

[43] Glyn, John: The discovery and early use of cortisone. In: J R Soc Med. 1998 Oct; 91(10), p. 515.

[44] Rook: 2012, pp. 133 - 134.

[45] No author information: Lexikon der Chemie (Encyclopaedia of Chemistry) – Nebennierenrindenhormone (adrenocorticosteroids), in: spektrum.de, URL: http://www.spektrum.de/lexikon/chemie/nebennierenrindenhormone/6203&_druck=1 (15. März (March 15,) 2016)

[46] Kendall: 1971, p. 114.

[47] Rook: 2012 p. 140.

[48] Carlisle, James M.: Cortisone (compound E); summary of its clinical uses. British Medical Journal. 1950; 2(4679): pp. 590-5.

[49] Rook: 2012 pp. 147 - 150.

[50] Poek, Klaus: Einführung in die klinische Neurologie (Introduction to clinical neurology), Berlin / Heidelberg / New York 1966, p. 272.

[51] No author information (Hg./ed. AMSEL / DMSG): Multiple Sklerose (multiple sclerosis) – Eine Zeitreise (a journey in time), in: geschichte-der-ms.de: https://web.archive.org/web/20140517134203/http://geschichte-der-ms.de/ (17.05.2014)

[52] Poek: 1972, p. 344.

[53] Poek, Klaus: Neurologie (neurology) – Ein Lehrbuch für Studierende und Ärzte (A textbook for students and doctors), Berlin / Heidelberg / New York 1978, 5. Auflage (5th edition), p. 264.

[54] Poek, Klaus: Neurologie (neurology), Berlin / Heidelberg / New York 1992, 8. Auflage (8th edition), p. 335.

[55] No author information (Hg./ed. Deutsche Rheuma Liga – German league for rheumatica): medikamentenfuehrer_3.1 (drug guide) – Kortison-Präparate (cortisone preparations), in: rheumaliga.de, URL: https://www.rheuma-liga.de/.../user.../medikamentenfuehrer_3.pdf (15.05.2016)

[56] Poek, Klaus: Neurologie (neurology), Berlin / Heidelberg / New York 1998, 10. Auflage (10th edition), p. 507.

[57] Hacke, Werner / Poek, Klaus: Neurologie (neurology), Heidelberg 2006, 12. Auflage, p. 498.

[58] Leitlinien der DGN 2008 (Guidelines of the DGN 2008) – Diagnostik und Therapie der Multiplen Sklerose (Diagnostics and treatment of multiple sclerosis), pp. 9 - 10.

[59] Schindler, A. E.: Endokrinologie des 2. und 3. Trimenon der normalen Schwangerschaft. In: Grundlagen und Klinik der menschlichen Fortpflanzung Endocrinology of the 2nd and 3rd trimesters of normal pregnancy. In: Fundamentals and Symptomatology of Human Reproduction) (Hgg./eds. Lauritzen, C. / Nieschlag, E. / Schneider, H. P. G.), Berlin / New York 1988, p. 154.

[60] No author information: Gramm (gram/s), in: Wikipedia, URL: http://web.archive.org/web/20160402182318/https://de.wikipedia.org/wiki/Gramm (02.04.2016)

[61] Göbel, Wolfgang: "Pregl, Fritz", in: Neue Deutsche Biographie (new German biography) 20 (2001), p. 685-686 [Onlinefassung – online edition], URL: http://www.deutsche-biographie.de/pnd11890986X.html

[62] No author information: Fritz Pregl, in: Wikipedia, URL: http://web.archive.org/web/20160408030326/https://de.wikipedia.org/wiki/Fritz_Pregl#Arbeit (08.04.2016)

[63] Göbel 2001: "Pregl, Fritz", pp. 685-686

[64]
a) ibid., pp.685-686
b) Szabadváry, Ferenc (dt. Übersetzung/German translation: Kerstein, Günther): Geschichte der analytischen Chemie (History of Analytical Chemistry), Braunschweig 1966, p. 208.

[65] No author information: Fritz Pregl, in: Nobelprize.org, URL: http://web.archive.org/web/20160505124243/http://nobelprize.org/nobel_prizes/chemistry/laureates/1923/pregl-bio.html (06.05.2016)

[66] Ibid.

[67] Hench / Kendall / Slocumb / Polley: Ann Rheum Dis. 1949 Jun; 8(2): p. 98.

[68] Arthritis, rheumatoide. In: Pschyrembel: 1994, pp. 117 – 118.

[69] No author information (Hg. Max-Planck-Institut für Psychiatrie (ed. Max-Planck-Institute for Psychiatry): Multiple Sklerose (MS) -- Die häufigsten Fragen: 11. MS und Schwangerschaft, in: Max-Planck-Institut für Psychiatrie (Deutsche Forschungsanstalt für Psychatrie), (The most common questions: 11. MS and pregnancy, in: Max-Planck-Institut für Psychiatrie - Max Planck Institute for Psychiatry (German Research Institute for Psychiatry), URL: https://web.archive.org/web/20131023120457/http://www.mpipsykl.mpg.de/clinic/erkrankungen/ms/index.html

[70] Dr. med. habil. Christoph Heesen (Universitätsklinikum Hamburg Eppendorf) in einem Interview mit der 3sat-Sendung „nano“; Beitrag „Heilige Medizin - Weihrauch heilt - Nebenwirkungen sind unklar“, gesendet am Montag den 16. September 2013, (University Hospital Hamburg Eppendorf) in an interview with the 3sat broadcast "nano"; Contribution "Holy Medicine - incense heals - side effects are unclear", broadcast on Monday, September 16, 2013), URL: http://web.archive.org/web/20160527071452/http://www.3sat.de/page/?source=/nano/medizin/171975/index.html (27.05.2016)

[71] Antwerpes, Frank / Mokli, Yahia / Sutter, Daniel Olivier: Multiple Sklerose (MS), in:

DocCheck Flexikon, URL:
http://web.archive.org/web/20150920011556/http://flexikon.doccheck.com/de/Multiple_Sklerose (20.09.2015)

[72] No author information: Schlaganfall: Radikales Umdenken in der Forschung nötig, in: Pressemitteilungen des Universitätsklinikums Frankfurt -- Goethe-Universität (Stroke: Radical rethinking needed in research, in: Press releases of the University Hospital Frankfurt - Goethe University), URL:
http://www.kgu.de/presse/pressemitteilungen/article/2013/01/07/schlaganfall-radikales-umdenken-in-der-forschung-noetig.html (01.06.2016)

[73]
a) Antwerpes, Frank / Römer, Gunnar: Experimentelle autoimmune Enzephalomyelitis (Experimental autoimmune encephalomyelitis), in: DocCheck Flexikon, URL:
http://flexikon.doccheck.com/de/Experimentelle_autoimmune_Enzephalomyelitis (28.05.2016)
b) No author information: Experimentelle autoimmune Enzephalomyelitis (Experimental autoimmune encephalomyelitis), in: Wikipedia, URL:
http://web.archive.org/web/20160513065948/https://de.wikipedia.org/wiki/Experimentelle_autoimmune_Enzephalomyelitis (13.05.2016)

[74]
a)Weihe, Wolfgang: Multiple Sklerose – Eine Einführung (MS – an introduction), 5. Auflage (5th edition), Bad Zwesten 2010, p. 147 – 148.
b) No author information: Freund-Adjuvans, in: chemie.de, URL:
http://www.chemie.de/lexikon/Freund-Adjuvans.html (28.05.2016)

[75] No author information: Magnetresonanztomographie (magnetic resonance imaging), in: Wikipedia, URL:
http://web.archive.org/web/20160428154709/https://de.wikipedia.org/wiki/Magnetresonanztomographie (28.04.2016)

[76] No author information: Multiple Sclerosis, in: Wikipedia, URL:
http://web.archive.org/web/20160414033333/https://de.wikipedia.org/wiki/Multiple_Sklerose (14.04.2016)

[77] No author information (Hg. DMSG): Maus und Ratte als Modell für Multiple Sklerose (Mouse and rat as a model for multiple sclerosis)?, in: DMSG, URL:
http://web.archive.org/web/20150716112448/http://www.dmsg.de/multiple-sclerosis-news/index.php?w3pid=news&kategorie=forschung&anr=4970 (16.07.2015)

[78]
a) Franklin, Robin J. M.: Remyelinisierung: das nächste Behandlungsziel bei MS (Remyelination: the next treatment target for MS)?, in: multiple sclerosis international federation, URL:
http://web.archive.org/web/20100626192641/http://www.msif.org/de/publications/ms_in_focus/issue_11_stem_cells_and_remyelination_in_ms/remyelination_t.html (26.06.2010)
b) No author information (Hg./ed. amsel): Umfangreiche Remyelinisierung bei Multipler Sklerose (Extensive remyelination in multiple sclerosis), in: amsel -- Das Multiple Sklerose Portal (The portal for multiple sclerosis), URL:
http://web.archive.org/web/20160529014430/http://www.amsel.de/multiple-sclerosis-news/medizin/Umfangreiche-Remyelinisierung-bei-Multipler-Sklerose_2339 (29.05.2016)

[79] No author information: Multiple Sklerose (multiple sclerosis), in: Wikipedia, URL:
http://web.archive.org/web/20160414033333/https://de.wikipedia.org/wiki/Multiple_Sklerose

e#cite_note-68> (14.04.2016)

[80] Glukokortikoide (glucocorticoids). In: Pschyrembel: 1994, pp. 553 – 554.

[81] Langer, H. E.: Prednisolon-Äquivalent (Prednisolone equivalent), in: rheuma-online, URL: http://web.archive.org/web/20140709012658/http://www.rheuma-online.de/a-z/p/prednisolon-aequivalent.html (09.07.2014)

[82]
a) Rau, R. / Wassenberg, S. / Zeidler, H.: Low dose prednisolone therapy (LDPT) retards radiographically detectable destruction in early rheumatoid arthritis, in: Springer Link, URL: http://link.springer.com/article/10.1007/s003930070026 (29.05.2016)
b) Langer, H. E.: Cortison Einnahmeempfehlungen (recommended cortisone intakes) – 3. Low-Dose-Therapie/therapy, in: rheuma-online, URL: https://web.archive.org/web/20140708090009/http://www.rheuma-online.de/medikamente/cortison/cortison-einnahmeempfehlungen.html (08.07.2014)

[83] Weihe: 2010, p. 160.