Patient-Based Medicine

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Treat the Patient, Not the Disease

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CHAPTER ONE

THE CONCEPT OF CLINICAL RESEARCH OR THE END OF DISCUSSION ABOUT PLACEBO AND SPECIFIC EFFECTS

Preliminary remark: It started with a thorough analysis
http://www.paracelsus-heute.ch/cms/literatur/011_wiss_einsiedler_symposium/0113.php

The reorientation of clinical research towards the questions of treatment benefit (beyond the question of treatment efficacy) and of how much clinical trials represent actual practice (external validity) is the timely path to clinical research questions of real interest and importance. Postmodern anything goes makes it possible to also consider hitherto dismissed effects, such as placebo, as valuable. However, that would require a precise documentation of the external validity of such effects. Not disease as such, but the disease context, not therapy as such, but the therapeutic context, not the patient as such, but the patient context, not a test as such, but the test situation has become an important focus of clinical research. In respect to test results, current medicine can and should recognize its preoccupation with allegedly objective and hard data. The patient context can determine whether an efficacious therapy is beneficial or harmful. It is thus the proper definition of the patient context which makes medicine documentable, no matter how objective or subjective the effect of therapy is. The consideration of the therapeutic context leads to the important distinction between efficacy and effectiveness (or benefit), and this makes it clear that the randomized controlled trial in its traditional design as the placebo controlled double-blind trial (DBRCT) is limited to the evaluation of drug theory. The evaluation of treatment effectiveness requires more pragmatic trials which study treatment operations and not isolated components and which may also compare entire treatment strategies. Pragmatic clinical trials, in future, will not only allow the study of pathogenesis blockers, but also the study of salutogenic interventions working with the host constitution. The focus of attention and research in the new school of EBM

with clinical epidemiology as its basic science, and not mere literature-based medicine, has long ago identified illness as the product of host, disease and environment. Meanwhile, the dispute about placebo and specific effects has become obsolete.

The title of the *3rd Scientific Symposium of Einsiedeln Placebo – Valuable if it Helps the Patient – Methods and Design of a Pragmatic Clinical Research, An orientation towards patient benefit* makes it clear that we will not only discuss speculations about the existence and nature of the placebo effect, but mainly the place of placebo in the context of clinical trials and clinical judgement. The debate as to whether placebo effects exist at all adds to the fact that not every seemingly unexplainable improvement is a placebo effect. The natural course of a disease, sometimes together with a regression to the mean, can lead to improvements, but this rather academic debate is of minor importance for our discussion. Often, placebo is called a non-specific effect. It remains difficult to define what is specific and what is not (see chapters II and III). Placebo is well-defined as a component of the placebo controlled double-blind trial, and its methodological place can be discussed. It is a fact that placebo, which has been disdained as mere conceit and excluded from our clinical thinking, is being rehabilitated.

External validity

With the onset of the age of clinical epidemiology and EBM, a reorientation of clinical research is taking place towards questions of treatment benefit (beyond the question of treatment efficacy) and of how much clinical trials represent actual practice (external validity). This is the timely path to clinical research questions of real interest and importance. Postmodern anything goes makes it possible to consider placebo effects as a valuable part of medicine, not disease as such, but the disease context, not therapy as such, but the therapeutic context, not the patient as such, but the patient context, not a test as such, but the test situation have become important foci of clinical research and critical appraisal of evidence. However, a documentation of the external validity of such effects must be included. What evidence/study result is important for my patient? Sacket et al. put the question everywhere, "*can you apply this [internally] valid, important evidence in caring for your [particular]patient?"* The dogma itself doesn't count, but the precise, empirically verified situation in which the dogma has its validity and results clearly doing more benefit than harm. This change in the understanding of medical science is more revolutionary than it looks and may be as significant as the end of the Middle Ages 500 years ago. It was

Paracelsus that recognized the importance of external validity. He observed that veneration of saints is helpful if it helps to face fear and uncertainty, but that the veneration business run by the church is illusionistic and detrimental to health. The most famous dictum of Paracelsus says: "everything can be venom or cure. The *dose* makes the difference." Dose can also be understood as the context.

Test and test context

Test results in current medicine must take into account that objective and hard data fails to account for spontaneous salutogenesis and the placebo effect. Dismissal of placebo as a medical non-value is based on the belief that modern, conventional medicine cannot take this into account because of the belief that only what is a *hard* and *objective* diagnostic finding is real. This, we tend to reason, makes our method superior to alternative quacks and to the imaginary placebos of earlier times. We will first touch on test and test context and patient and patient context before delving into therapy and therapeutic context. This will then lead into placebo and its place in clinical trials. One can thus elucidate that modern medicine is not necessarily more enlightened than the medicine of earlier times. The pre-test likelihood has the same mathematical power as the technical specificity to influence the post-test likelihood or positive predictive value which is the relevant measure in practice. If the pre-test likelihood is 1 in 100, the false positives will be multiplied by 100 (figure 1). Thus, it is the proper enquiry of the patient history which makes medicine scientific, no matter how objective or subjective the test results may be. If the clinical suspicion of a certain diagnosis is high, then a positive test result means an almost certain confirmation of the diagnosis. If there is no real clinical suspicion as in screenings or in a check-up, a positive result is often false and not much different from the pre-test likelihood. This is the main reason why screenings and check-ups are increasingly viewed as useless as the positive predictive value is not much different from the pre-test likelihood. For example, if there is a high clinical suspicion of coronary heart disease CHD – let us estimate the likelihood to be 1 to 1, a positive result in the exercise ECG will increase the likelihood to 80% (sensitivity is about 70% and specificity 80%) which makes the test rather useful in this situation. If we use the same test in as a check-up in a younger man with no symptoms – let us estimate the likelihood of being 1%. The positive predictive value with the very same result will only be 4%. In more than 95% of cases, the result will be a false positive. The test does not give us useful information. Another example: a negative mammography result in a woman of about 60 years

results in a negative predictive value of 99.8%. She is then 99.8% certain that there is no hidden breast cancer that will become apparent in the next 2-3 years. We are happy about this certainty. However, since the incidence is very low, we are already 99.5% certain without mammography that there will be no cancer.

Figure 1.

		Disease			
Test	True positive	a	c	False positive	Test positive
	False negative	b	d	True negative	Test negative
		Diseased		Healthy	

Sensitivity = a/a+c
Specificity = d/b+d
Positive predictive value (PPD) = a/a+b
Negative predictive value (NPD) = d/c+d
Prevalence = a+b/a+b+c+d

We do not need to apply screening technology to assure us. We do not need to create the risk of false positive results and overdiagnosis. With Paracelsus we can say: futile veneration of saints (in modern clothes). This may show how illiterate and fallacious the ordinary belief is in hard and objective results that leads to modern medicine wrongly believing that we know better than the good doctors did hundreds of years ago.

Patient and the patient context

The patient context determines whether an efficacious therapy is beneficial or harmful, and therefore, it is the proper definition of the patient context which makes medicine scientific, no matter how objective or subjective the effect of a given therapy may be. The existence of a true, confirmed pathological finding does not tell how sick a patient is. The patient context is as much a result of the *base-line risk*. This determines the *number-needed to treat* which is the measure of the absolute risk reduction that can be expected. The very same therapy can be beneficial in a severely diseased person, but harmful in a lightly diseased person. An example: if I treat a woman with severe osteoporosis who has a chance of 50% to suffer a bone fracture within 1 year with a bisphosphonate, which will likely reduce the risk by 50%, she will have a benefit with a chance of 50% or 1:2 respectively. The number needed to treat is only 2 (figure 2). If I treat a healthy woman with no symptoms, but with a low densitometry result which was measured because of the modern

densitometry propaganda, the risk is maybe only 2%. It can also be reduced by 50% from 2% to 1%. The number needed to treat is now 100. In the first case the therapy may mean a significant relief, but treatment in the second case will mean possible long-term adverse effects with no clear benefit. The mathematics of the baseline risk and NNT is simple. You have only fully understood the issue when you become aware that the treatment of high blood cholesterol in low-risk persons is less efficient than the treatment of normal blood cholesterol in high-risk persons. The well-known Framingham data illustrate this clearly (figure 3).

Figure 2. Number needed to treat NNT as a function of the extent of risk reduction and the baseline risk.

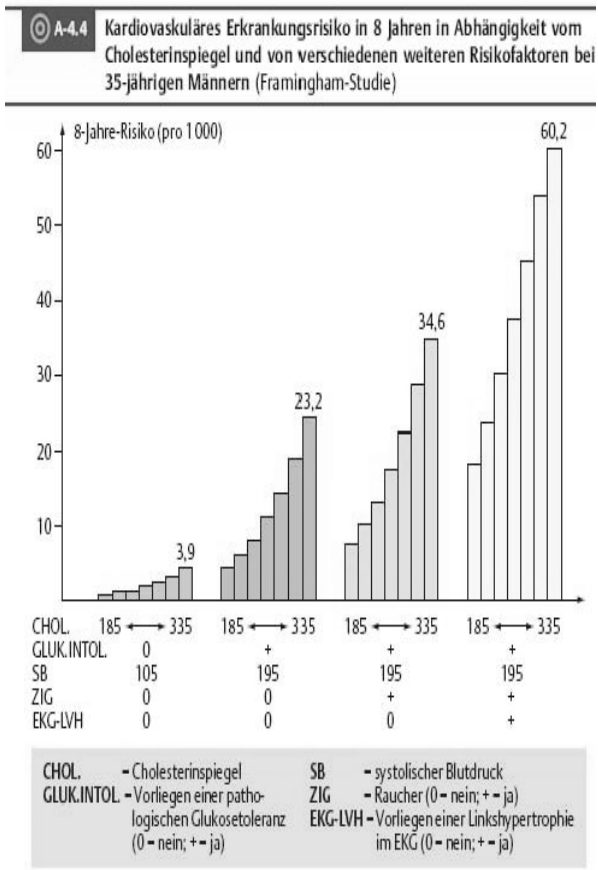


Figure 3. Cardiovascular risk during 8 years depending on multiple risk factors – blood cholesterol, glucose intolerance, systolic hypertension, smoking. Left ventricular hypertrophy. Framingham study 1979.

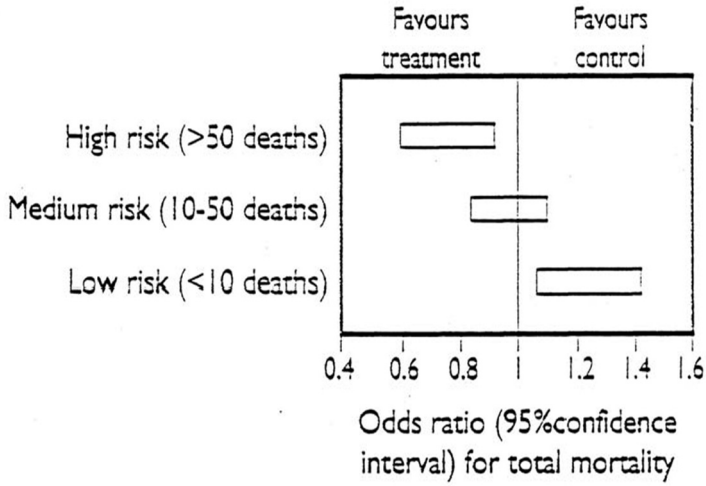


FIG 4—*Effect of cholesterol lowering treatment on total mortality stratified by number of deaths from coronary heart disease per 1000 person years in control subjects*

phy – Framingham study 1979

It is obvious that the risk levels from low to high blood cholesterol are considerably higher if there are risk factors other than blood cholesterol. Lowering blood cholesterol has a greater effect on the risk if the overall risk is high. The notion of normal and pathological cholesterol levels is a fallacy that ignores the probabilistic nature of the risk factor model. The Sheffield Table forms a more adequate approach. They do not assume that there is a cut-off level between normal and pathological cholesterol values, but that we think of persons with elevated risk levels and persons with safe levels that do not require treatment, depending on the overall risk. One could speak of a total risk cut-off level instead of a cholesterol cut-off level. The Sheffield authors chose an arbitrary CHD risk of 3% annually which results in NNT of 100. Persons within these boundaries warrant a regimen of risk factor reduction. Outside the boundaries the total risk is small and the NNT excessively high.

Without a thorough analysis of the context, patients run into the arms of death – led by the race horses of modern medicine. *George Davey Smith* presented his findings on the total mortality effect of cholesterol lowering treatment at the 1st Scientific Symposium of Einsiedeln. He showed that cholesterol lowering treatment increased total mortality in low-risk persons and could only decrease total mortality in high-risk persons (figure 4). Cholesterol lowering treatment reduces mortality to a greater extent than it reduces infarct mortality (Johannes Schmidt. Cholesterol lowering treatment and mortality. Br Med J. 1992:305:1126-1127). It is not surprising that a low total risk and a corresponding high NNT means a cumulation of adverse effects with a possible unintended mortality increase. Cholesterol screening was a bad idea and harmful to many people. Do-gooders can have negative effects in the hands of modern medicine. Alternative practitioners as well as conventional doctors of medicine must use the patient centered parameters to make sure that therapy is beneficial and not harmful.

Figure 4. Effect of cholesterol lowering treatment on total mortality stratified by number of deaths from coronary. heart disease per 1000 person years in control subjects. George Davey Smith. Einsiedeln Symposium, October 1993.

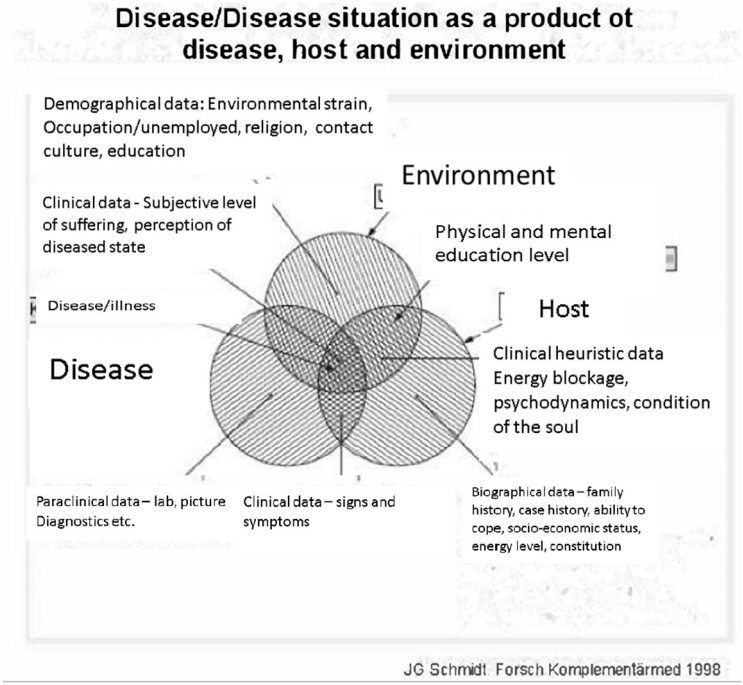


Table 1. Sheffield Table of primary prevention of CHD, The Lancet 1996.

THE LANCET

Men: cholesterol concentration (mmol/L)

Hypertension	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	Yes	No
Smoking	Yes	Yes	No	No	Yes	Yes	Yes	No	Yes	No	No	No
Diabetes	Yes	No	Yes	No	Yes	Yes	No	Yes	No	Yes	No	No
LVH	Yes	Yes	Yes	Yes	No	No	No	No	No	No	No	No
Age (yr)												
70	5·5	5·5	5·5	5·5	5·5	5·5	5·5	5·5	5·5	6·0	6·5	7·7
68	5·5	5·5	5·5	5·5	5·5	5·5	5·5	5·5	5·6	6·4	6·9	8·2
66	5·5	5·5	5·5	5·5	5·5	5·5	5·5	5·7	5·9	6·8	7·3	8·7
64	5·5	5·5	5·5	5·5	5·5	5·5	5·5	6·1	6·3	7·3	7·8	9·3
62	5·5	5·5	5·5	5·5	5·5	5·5	5·6	6·5	6·7	7·8	8·3	
60	5·5	5·5	5·5	5·5	5·5	5·6	6·0	6·9	7·2	8·3	8·9	
58	5·5	5·5	5·5	5·5	5·5	6·1	6·5	7·4	7·7	8·9		
56	5·5	5·5	5·5	5·5	5·5	6·5	7·0	8·0	8·3			
54	5·5	5·5	5·5	5·5	5·9	7·0	7·5	8·6	9·0			
52	5·5	5·5	5·5	5·5	6·3	7·6	8·1	9·3				
50	5·5	5·5	5·5	5·7	6·9	8·2	8·8					
48	5·5	5·5	5·5	6·2	7·5	8·9						
46	5·5	5·5	5·5	6·8	8·2							
44	5·5	5·5	5·8	7·4	9·0							
42	5·5	5·6	6·4	8·2								
40	5·5	6·1	7·1	9·0								
38	5·5	6·8	7·9									
36	6·0	7·6	8·8									
34	6·7	8·6										
32	7·6											
30	8·7											
28												

Women: cholesterol concentration (mmol/L)

Hypertension	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	Yes	No
Smoking	Yes	No	Yes	Yes	No	Yes	No	Yes	No	Yes	No	No
Diabetes	Yes	Yes	No	Yes	No	Yes	Yes	No	No	No	No	No
LVH	Yes	Yes	Yes	No	Yes	No	No	No	No	No	No	No
Age (yr)												
70	5·5	5·5	5·5	5·8	6·3	6·9	8·5	9·8				
68	5·5	5·5	5·5	5·8	6·4	7·0	8·6	9·9				
66	5·5	5·5	5·5	5·9	6·5	7·1	8·7	10·0				
64	5·5	5·5	5·5	6·1	6·6	7·2	8·9					
62	5·5	5·5	5·5	6·2	6·8	7·4	9·1					
60	5·5	5·5	5·5	6·4	7·0	7·7	9·4					
58	5·5	5·5	5·5	6·7	7·3	8·0	9·8					
56	5·5	5·5	5·5	7·0	7·7	8·4						
54	5·5	5·5	5·5	7·4	8·1	8·9						
52	5·5	5·5	5·9	7·9	8·7	9·4						
50	5·5	5·5	6·4	8·5	9·3							
48	5·5	6·0	6·9	9·3								
46	5·5	6·7	7·7									
44	5·5	7·5	8·6									
42	5·8	8·5	9·8									
40	6·7	9·9										
38	8·0											
36	9·7											
34												

Sheffield table for primary prevention of CHD

A patient whose value falls in the area with no entries has an estimated risk of coronary events of less than 3·0% per year

Notes on use of table

- Do **not** use for decisions on **secondary prevention:** patients with myocardial infarct, angina, peripheral vascular disease, or symptomatic carotid disease already have high CHD risk
- At this CHD risk (3% events per year) treatment with a statin (but not necessarily other drug classes) is justifiable
- The value of cholesterol reduction at <5·5 mmol/L or age >70 years is not established
- Use table **after** appropriate advice on smoking, diet, and control of systolic blood pressure to ≤160 mm Hg
- Use the **average** of two or more cholesterol concentrations
- Consider **individual** factors (eg, low high-density-lipoprotein cholesterol or bad family history), in final treatment decisions
- The table is valid for UK, Northern European, and North American populations—Southern European and Far Eastern populations have **lower** CHD risk in relation to the standard risk factors

Instructions

- Choose the table for men or women
- Identify the correct column for smoking, hypertension, diabetes, and left ventricular hypertrophy (LVH) by ECG
- Identify the row showing the age of the subject
- Read off the cholesterol concentration at the intersection of the appropriate column and row:

If there is no entry, **cholesterol need not be measured**

If there is an entry, **measure serum cholesterol**

If the average cholesterol on repeated measurement is at or above the level shown, the CHD event risk is ⩾3·0% per year—**consider treatment**

The table can be used to **look forward** to possible need for measurement or treatment at an older age

Persons in the white part have a CHD risk of less than 3% per year, even if the blood cholesterol is very high. In this cohort, blood cholesterol testing does not make much sense. In Switzerland and Germany, the risk is only half of that in Britain and in the US. We can apply the Sheffield Table for women as well as for men.

Petr Skrabanek told us the following Persian story at the 1st Scientific Symposium of Einsiedeln 1993: *An old master is surprised by his young gardener who comes to ask him for his fastest horse) as he has to be away tonight. The old master asked him why he was so excited) has something happened? The gardener told him he saw Death while he was working in the garden) and Death threatened him. He realized he had to hide on a farm) otherwise Death would get him. The master gave him the horse and the gardener rode away to the farm. Later, the master was walking through the garden) and he also saw Death. He asked Death why did you threaten my gardener? And Death replied, "I was not threatening him. I just wondered what he was doing here as I was supposed to meet him tonight on the farm."*

This story nicely illustrates our modern problem with pathological findings. If every shady abnormal finding is seen as a threat that must be combatted, doctors and patients keep busy running away from Death – in a "folie à deux".

Therapy and therapeutic context

The discussion of therapy and therapeutic context leads us now directly to placebo in clinical trials. Alvan Feinstein put it forward at the 1st Scientific Symposia of Einsiedeln, that the role of the doctor is primarily to alleviate and comfort according to the old French aphorism: *Guèrir quuelque fois, Soulager souvent, Consoler toujours*. Feinstein was critical of modern medicine in that it looks down on the tasks of alleviation and consolation and limits itself to organ repair (the so-called apparatus error model). He emphasized the need of a nosology of placebo effects. The first time I had to deal with placebo in clinical trials was the acupuncture congress 1992 in Rome. I was faced with a few questions of how to design controlled trials for acupuncture. I found many studies using sham acupuncture, but this may be a wrong way to go. The doctor and his way of thinking may have a strong placebo effect. The instruments used (acupuncture needles) are perhaps merely vehicles of these effects. Because of technical difficulties, surgery does not generally use sham surgery as a control – there are only a few exceptions. The placebo control, in the end, is a method with questionable

external validity in studies of acupuncture and many other techniques. The question of whether a given therapy is specific or non-specific has little other than theoretical value. The patient is interested how effective, sustainable, safe and costly a therapy is. *Bradford Hill* said in 1963: "If there is a treatment of accepted value, the question whether to use a placebo will hardly arise, for the doctor will wish to know whether a new treatment is more or less effective than the old, not that it is more effective than nothing" (quoted by *Kenneth Rothman* in an editorial with the title Placebo-Mania, BMJ 1996).

The questionable validity of placebo-controlled trials has barely been addressed by the new school of EBM, probably because a methodological confusion prevails. Many academics are hesitant to be identified with placebo effects, and they do not realize that the uncritical perpetuation of placebo controls is not in the interest of the patient. An elucidated understanding of placebo controls is not easy because conventional academic medicine is preoccupied with the concept that alternative medicine, such as homeopathy, chiropractic treatment and light therapy is quackery. Academic medicine ignores for the most part superstitious beliefs, although some inroads have been made. The instrument of the controlled trial by Archie Cochrane, no doubt, is the best standard we have to test therapies – entire therapeutic settings and pharmacological agents. The DBRCT is the best we have, but we must keep in mind that a placebo-controlled trial is a special design to test isolated pharmacological factors. Alvan Feinstein accurately demonstrated in his 1987 book *Clinimetrics* that there is a fallacious academic tendency to understand specificity as scientific evidence. Specificity, however, is often at the cost of sensitivity. Modern medical science is not always relevant for the practice of medicine. It is important to understand that clinical studies need to apply an intelligent compromise between the sensitivity and specificity of therapies. The literature describing pragmatic, practice-sensitive study designs is still scarce. Randomized trials (Simon 1995) or randomized trials with individualized therapies (Holle et Pritsch 1996) are common. The placebo-controlled trial is overly specific and not sensitive enough for practice relevance. The school of EBM does not seem to have internalized this.

Disease and disease context

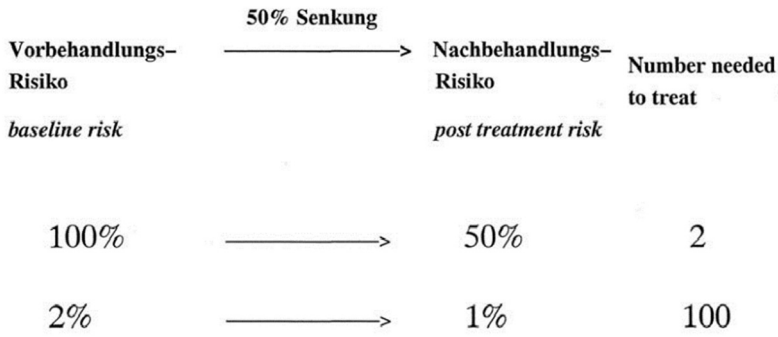
It may be helpful to first address the question whether modern medicine has overcome and left behind exorcism. We have seen how much exorcism of threatening findings through cholesterol screening, for example, is flourishing. We tend to assume that exorcism, like treating patients based on blood cholesterol tests, can be useful. The problem is a fear-based instead of knowledge-based, no matter if we use old or modern techniques. The medical handling of cancer, similarly, seems to follow the priestly reflex to segregate the malign devil (the cancer) which is in fact also part of God's creation. Argument and dispute would be more helpful than segregation. Since the nineties of the last century there is ample evidence about the scarce effect of medical cancer cell removal as there is little effect of local cancer eradication on mortality (table 2).

Table 2. Breast cancer eradication and mortality.

Radical surgery	<->	minimal surgery	
no difference Local radiation	<->	no radiation	
no difference Minimal surgery	<->	no surgery	not known

All the traditional breast cancer treatments have severe adverse effects, but the ideas of treatment are rather mystical and there is a lack of good evidence that they do less harm than good. Feinstein has shown that the patient context, i.e. how is the patient able to cope with daily activities – is more important for the prognosis than histology and TNM stage. Some soft clinical interventions such as psychosocial support and palliative care could turn the disease from a malignant into a more benign course. Illness is always a product of disease and host resistance (figure 5). Conventional medicine focuses on supposedly objective diseases whereas complementary medicine and psychotherapy rather focuses on the host and education/ formation of the host. It appears that placebo has an effect on host formation. Whether host formation leads to a beneficial effect can be studied in pragmatic clinical trials just as much as it can and should be studied whether pathogenesis blockers – betablockers, antidiabetics, ACE inhibitors, serotonin antagonists etc. do more harm than good and in what context. In principle, the methodology for complex clinical trials exists today and it is evident that clinical research can and should study the great variety of interventions to find what is beneficial for the patient. It is of lesser importance whether it has a label of placebo or specific or somatic or psychic or functional therapy.

Figure 5. Disease context/illness as a product of disease, host and environment.



Bildung = formation/education
Demographische Daten = demographics: ecological damage, climate, employment situation, religion, culture, education system
50% Senkung = 50% reduction

A pragmatic nosology

The modern clinical research methodology has already said farewell to the discussion about placebo and specific effects. There remains the difficult task to develop step by step a new nosology of the host and of disease contexts which allow prognostic information and the definition of which therapy is best indicated. We are quite confident that the work of a further development of a pluralistic EBM will be the future of medicine.

CHAPTER TWO

IS RENUNCIATION OF INTERVENTION ALWAYS NIHILISM? A RATIONAL MEDICAL PRACTICE BASED ON EVIDENCE

Preliminary remark: During my professional life, a number of essays and speeches occrued which all deal with the central aspect of modern medicine: the patient. As an author of clinical epidemiology and EBM, I increasingly realized that the main theme of EBM was the new look at the patient as the object of medicine. Supporting salutogenesis as much as fighting disease and pathological findings is the route medicine has to travel (again). The first time this issue became apparent to me was when I prepared an invited speech at The German Congress of Internal Medicine chaired by Johannes Koebberling. It was released in a book edited by Koebberling in Springer Publishing, Berlin 1998: „Zeitfragen der Medizin". Here is my English translation.

Speech by Johannes Schmidt delivered at the German Congress of Internal Medicine, Wiesbaden, April, 1997. First published in J. Koebberling. Zeitfragen der Medizin. Springer Berlin Heidelberg 1998
http://www.paracelsus-heute.ch/cms/literatur/PDF/Springer1997.pdf

The critical appraisal of scientific evidence in medicine is going through a striking transformation. Up until now, a pathophysiological improvement in the patient was considered evidence for effectiveness and patient benefit, but methodological progress has made it clear that we must also gather evidence of a reduction in morbidity and patient mortality and of improvement in the overall quality of life. The effect of the intervention must be significantly demonstrated, and expressed e.g. in the number-needed-to-treat. Such a rational and critical appraisal is often faced with the reproach of being *nihilistic.* To accept medical powerlessness and to engage in medical activism, meanwhile, could be the most important

development of medicine in the coming decades. This is something, because we now have study results that show, for example, that breast cancer can lead to an improvement of the quality of life despite the physical ailment, as spiritual growth and consolidation of relationships occur.

If I consider the short time between my undergraduate medical education and today – just 15 years – a striking change in the appraisal of medical effectiveness and benefit has become apparent. In recent times, the catchword EBM is the term used for this change. The corresponding scientific methods of clinical epidemiology have been formulated for some time, but the rapid propagation of EBM seems to demonstrate that among many medical scientists, the notion has found acceptance that conventional university medicine has not been based on proper scientific evidence, but on credence and opinion.

Cognition and the corresponding nature of evidence

Of course, the medical community has attempted to base their doctrines on the available evidence long ago, but the methodological progress in clinical epidemiology has led to a change in the criteria of what can be considered as valid evidence. A positive change of laboratory or imaging findings was generally considered evidence of effectiveness. Now we request evidence of a beneficial change in patient parameters such as morbidity, mortality and quality of life. We further request results of controlled trials that show a difference in these parameters that is enough to result in a reasonably low number needed to treat (NNT). Physiological mechanisms of action are theorized, but they have a low rank in the current hierarchy of evidence.

I am aware that I speak to internists and specialists in internal medicine today. I can assume that the CAST trial is well known. This well designed trial has shown us how greatly we had been misled by pathophysiological reasoning that was based on insufficient studies suffering from selection bias. Uncontrolled cohort studies seemed to demonstrate that patients with ventricular arrhythmia had a far better prognosis if the arrhytmia was successfully suppressed by medicine. Arrhythmia which is easily supressable is not the same as arrhythmia that is not. No two patients are the same, and yet we hurtle headlong into categorization of patients in groups that can be treated the same. The cohort studies mistakenly compared different patients and not different treatments. CAST showed

that the drugs could effectively supress arrhythmia and make the ECG look normal, but that mortality was 3-fold under the active treatment. CAST is perhaps the classic study to inform us of the surrogate fallacy, i.e. the observation that improving the ECG is not the same as an improvement for the patient.

What activities are possible in this time of methodological change? It is a very fascinating professioal challenge. You can choose to stay safe with the great majority of indifferent colleagues - which may in turn carry the risk of sitting suddenly on a historic steamboat instead of a modern jet. Instead, you could start to distinguish which evidence is solid and unbiased from lower level evidence which may be faulty, and to distinguish quantitatively important effects from effects which operate in 1 of 100 or only 1 in 1000 patients, and thus become irrelevant (see e.g. [3]).

Fallacies in the current management of cancer

I ask for your acceptance that I use oncology to illustrate the change of scientific reasoning. Cancer leaves no one aloof and creates emotions. It is often the reason for extensive diagnostic activities with little benefit. We must do all we can and apply every medical means, because otherwise we could be accused of nihilism. I want to provoke you and state that the medical management of cancer – I will use breast cancer as example – appears to follow a rather cultural reflex of devil exclusion rather than a careful consideration of biological evidence. If we have something that seems to be able to combat cancer, we have considered it as evidence. This proposition may be a bit black and white, but I use it for the purpose of elucidation.

It occurred to me that we should look back and consider the great success of modern developments in abolishing infectious diseases to a great extent. In table 1 I have compared breast cancer with tuberculosis. In the case of tuberculosis, we have learnt that the host condition matters. There are no aggressive and less aggressive tuberculosis bacteria, but differences in the host. The same we could assume for breast cancer cells. In fact, we know that there are healthy breast cancer cell carriers as autopsy studies reveal. The strength of the host may also matter in cancer and perhaps we can find more progress in this direction.

CHAPTER THREE

LOW LEVEL LASER THERAPY AND MYOFASCIAL PAIN

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Abstract: An effective treatment modality leading to freedom from pain for whiplash syndrome, tension headache and post-concussion syndrome is presented. The background and theoretical basis of low-level laser therapy is presented. 5 cases representing patients treated with low level laser therapy are reported. The need for financing is discussed.

Keywords: inflammation, myofascial pain, whiplash syndrome, tension headache, post-concussion syndrome

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Introduction

There are at least 300,000 and possibly 500,000 to 600,000 Danes suffering from more or less chronic myofascial (myos is Greek for muscle and fascie is Latin for ligament) pain. This figure is gleaned from my experience as a municipal medical consultant with approximately 10000 cases over my table, where about half of these had myofascial pain syndromes as their presenting issue – whiplash syndrome, tension headache, post-concussion syndrome, lower back pain and many others. The number is derived by taking the percentage of the population locally and multiplying this by the total population. The most common and well-known examples of

myofascial pain are whiplash syndrome, post-concussion syndrome, and tension headache. This is a very poorly researched area, and my observations are based on my own experience. Other less common myofascial pains include frozen shoulder, mouse arm, tennis and golf elbow, lower back pain, facet joint syndrome, groin pain, bursitis coxae, unspecific joint pain in general and unspecific muscle pain. I have been unable to find literature to document this. This also is based upon my own experience. All of these syndromes are characterized by a lack of specific treatments and so far, no generally applicable, effective solution has been described. Again here, there is no literature documenting this, but the issues are plain for anyone dealing with these patients. This article has 3 purposes. The first is to describe the importance of examining the condition of the muscles when facing patients with myofascial pain. The second is to describe low-level laser therapy (LLLT) as an effective therapeutic form for myofascial pain, and the third is to illustrate the effect of this treatment with some examples.

No one knows how many patients with tension headache have been diagnosed with migraine, but there is no doubt that this misdiagnosis exists. This is again one of those truths that everyone knows, but the no one has been able to document. This is one of the common elements of our methodology, that we are perfectly capable of documenting what we do right, but horribly incapable of documenting what we do wrong, is wasteful and/or deleterious for our patients. The main reason for this misdiagnosis is the lack of examination of the condition of the neck muscles, which is the cause of tension headaches. In my experience, none of the patients I have examined have ever had their neck muscles examined by any of up to 35 different doctors and other therapists. Examining the muscles of the neck, one can determine whether or not platysma, the scalenes and trapezius muscles have normal consistency or, as is the case with patients with tension headaches, have increased tension and often with myoses. It takes a little training to complete a sufficient examination, but everyone with reasonable fingertip sensibility, knowledge of anatomy and pathophysiology can easily learn to do a qualified exam of the tension status of the neck. Specifically, myoses on the medial scalene can cause visual disturbances that contribute to the misdiagnoses[1].

The examination technique requires palpation of the named muscles with a light hand, so that the muscle structure can be felt through the skin. It is decisive to examine the entire muscle. There is often a significant difference from side to side, which makes the discovery easier, as the difference is

clearly felt. I find it most expeditious to do the exam on a gurney with a head holder so that the patient relaxes as much as possible during the exam.

Once such tensions have been established, there is a basis for referring to a clinic with experience in resolving the tensions. When the tension is resolved, the symptoms disappear. This is evidenced by my experience.

The past efforts have not been satisfactory. Although also not based in the literature, no treatment modality to date has been successful. The same applies to tension states that cause pain in other body parts than in the neck and in the head. It is clearly more difficult to detect tension in the deeper muscles, but a thorough history and prior examination with blood samples (exclusion of cancer, rheumatoid arthritis and vitamin D deficiency), ultrasound, X-ray, CT and/or MRI scan, which exclude more serious causes of pain, are usually negative in myofascial pain patients. When all studies show normal results, one can conclude that muscle tension and/or inflamed tendons and/or joints are the cause of the pain.

LLLT made its debut in Hungary in the early 1960s. A Hungarian surgeon Edre Mester (EM) has been credited with using it for the first time[2]. It was shortly after the ruby laser was put into use. During experiments with mice where he wanted to demonstrate the effect on induced skin tumors, which he could not detect. However, he noted a difference in the hair growth rate in the treated group compared with the untreated group[3]. Since then, attempts have been made to use LLLT over a number of conditions, of which myofascial pain is the area where the greatest effect is achieved[4]. There are numerous laser devices on the market, but the device that is best documented and with EU approval is LX2 from Thor Laser in the UK. LLLT has been the subject of study at the Harvard University School of Medicine, which has published an account of the mechanism of action[5]. It is a biphasic light source with a visible element of 720 nm and an invisible laser light of 613 nm. The visible light does not penetrate the skin, but the laser beam reaches 5-6 cm under the skin, depending on the tissue type[6]. There is no complete clarity on how it works, but there is no doubt that it acts as a powerful antioxidant locally. The role of antioxidants in reducing inflammation is well described[7]. It is less clear that myofascial pain is dependent on inflammatory processes, but what else should it be? How LLLT is anti-inflammatory is further described[8].

The muscles reveal varying degrees of affection by stress. It can be purely mental stress that affects the muscles and various physical stresses that

become chronic pain syndromes. Head trauma, including concussion and whiplash, affects the neck muscles in varying degrees of severity as tension and/or myoses in the neck region. There is no obvious logical explanation for why post-concussion patients have the same tensions in the neck as whiplash patients, but that this is the case is clear to anyone working with both groups[9],[10].

A patient who could probably have been cured, but who could not afford the treatment, and where the municipality would not provide subsidies, is explained below. Most of us have met such patients, and the attitude is generally that one must learn to live with it.

A middle-aged man was hit some years ago by a car that did not yield as it should, while the man was riding on a scooter. The collision was so forceful that the patient was thrown over the car and landed first on his head, then on his left shoulder. The helmet he was wearing shattered. He was whisked to the emergency room, which did not find any broken bones or evidence of internal injuries, and he was sent home. In the weeks following the accident, the symptom complex that the patient was afflicted by developed. The symptoms are severe, constant back pain, left shoulder and upper arm pain, and fingers that sleep more or less constantly, which is most pronounced on the left side. In addition, he suffers from dizziness almost constantly, which is worst when he is tired, and frequent headaches. He needs rest often, but cannot find peace. He sleeps badly at night due to pain and tension, and must often rest during the day for that reason. From the objective examination: The body from the diaphragm and below is unaffected. The left arm can be moved slightly backwards, but not to the opposite hip. It cannot be pressed over the horizontal passively (due to pain) or actively. Good strength over the elbow, wrist and fingers. Right arm is normal. All the muscles in the neck are very sore, and with pronounced myoses in the playtysma, scalenes and trapezius, which are hard as wood on the left side and quite firm on the right side. Down the back, all muscles are very tense and hard from the top down to the sacroiliac joint, no soreness below this level.

This was a pronounced muscle-related problem with severe myoses, which had been attempted treated with physiotherapy and painkillers without effect. The condition is treatable with LLLT and massage. At least 30 treatment sessions would have been necessary, presumably taking 45 minutes per session although more treatments cannot be ruled out, depending on the result. The end-result would probably have been full recovery and return to workability, but at least a significant improvement

would be achieved, and most likely a freedom from medication. The patient wanted to give the treatment a try, but since there was no financing available, the case did not continue.

Methods

Treatment with LLLT is delivered via a probe which is placed on the skin over the target muscle. It is not important that the skin is bare, but it does help to identify the underlying structures. The apparatus has two settings that are adjustable, that is the frequency of the flashes of the given light and the duration of the treatment. The frequency can be set from 2.5 Hz up to continuous over 12 increments, and the duration can be between five seconds and five minutes, also over 12 increments. Only two of the settings were used in this study, that is 2.5 Hz lasting 30 seconds, and continuous lasting two minutes. Treating a whiplash patient, which typically takes half an hour, typically includes a full treatment for all three scalene muscles, and varying portions of platysma and trapezius. These are treated with 2,5 Hz for 30 seconds per site. C3, C4, and C5 are given continuous light for 2 minutes per site. The probe heats up during use, but not to a dangerous level. It heats up to about 39°C before giving off as much heat as it creates. The tolerance of this heat varies extremely in patients. I switch between two identical probes so that one can cool off while the other is in use. A 40 mm probe delivers 1 W and penetrates 5 to 6 cm under the skin. A 65 mm probe delivers 1 W and penetrates approximately 1 cm under the skin. Experience dictates that treatment every other day is optimal. The duration of the treatment in terms of number of sessions varies extremely, from 10 to over 100 sessions until the patient is free from pain. Meanwhile, an average number is from 30 to 40. To date, no damage or side effects have been reported with LLLT. The only danger that has to be prevented is looking directly into the laser beam which can damage the retina.

Data Analysis

Simple collation

Results

There have been 178 patients in my clinic until now, and of these 25 with whiplash syndrome, 19 with post-concussion syndrome, and 23 with tension headache. All of these patients have become pain-free, none of them have relapsed. The rest of the patient population is a mix of various diagnoses,

all of which have myofascial origins. There have been a number of scar tissue patients, and patients with eczema which have all improved significantly. None of the patients have continued with the same medicine that they took when they came to the clinic after ended treatment. This attests to the power of the treatment. Some patients have presented with pain syndromes that do not make any sense in a traditional medical model, but LLLT helped them nonetheless.

The following 5 examples will illustrate the effect of treatment with LLLT. These have been chosen to represent their case type. Any of the N=178 could have been chosen. The point is to illustrate the power of the treatment.

Patient No. 1 was a young man who had fallen off a horse 4 years earlier and had hit his head and neck and his back on the hard ground underneath. There were no immediate signs of major damage and no visible wounds. In the weeks following the fall, the boy developed a severe, constant headache, which was the subject of numerous studies. Among other things, a syringomyelia was detected at the L1 level, low pressure in the spinal canal and a moderate Scheuermann. None of these conditions could be linked to the headache. Various neurosurgical departments, pediatric wards and other specialists had found and accepted indication for treatment with Tradolan, Ibumetin and Paracetamol as well as Omeprazole to protect against the side effects of the Ibumetin. There was no focus on the neck muscles. On one out of approximately 100 pages of documentation in the case, there was one sentence describing the tense neck muscles by a physiotherapist. This passage did not have any consequence that one could glean from the documentation. When I met the patient, he had a very knotty neck, where especially the medial scalene was a chain of myoses, which was extremely sore. There were, as is usual for this type of patient, large myoses in trapezius both near the cranium and in the mid-clavicular level (MCL). After a series of treatments with LLLT and massage and the physical training I directed for the patient, he was completely free of the medicine and had a slight headache approximately once a week that did not require medication. His neck muscles were without myoses, but still a little tense. The treatment was completed 2 years ago, and the condition has remained pain free.

Patient no. 2 is a middle-aged man who 2 years before the exam in my clinic, was involved in a classic rear-end collision that hit the patient's car with such speed that neither of the cars could drive from the scene of the accident. The patient was wearing a seat belt and airbags were released. As usual for these cases, the primary examination at the hospital was without special

findings. Approximately one year after the accident, the patient was awarded 8% disability and had been diagnosed with incipient dementia due to his reduced memory and concentration (common accompanying symptoms of whiplash syndrome). Again, no one in the process had examined the patient's neck muscles. When I met the patient, he had severe tension in the neck muscles and myoses in the medial and posterior scalenes as well as in the trapezius near his cranium and in the MCL. After a series of 32 treatments, he had become pain free, his neck muscles relaxed, and he had regained his memory and concentration. The treatment was completed 3 years ago and the condition has remained pain free.

Patient No. 3 was a young woman suffering from whiplash syndrome after two rear-end collisions. She had constant headaches, strained neck muscles and was depressed all the time. After a few treatments she felt much better, and her treatment could end after 9 sessions. The patient had no longer any pain and a relaxed neck. She had regained her energy and was happy again (an unusually short process). The treatment was completed 3 years ago and the condition has remained pain free.

Patient no. 4 was a middle-aged man who suffered a concussion of medium severity approximately 3 years previous to his appearance in the clinic. He had been examined by neurologists, neurosurgeons and his own GP and treated with various measures, including physiotherapy and strong painkillers. He suffered from severe, daily headaches, difficulty in concentration and memory and pain in the neck and back. His physical condition made him so depressed that he had seriously considered taking his own life. After approximately 10 treatments, his medication could be reduced. The headache and neck tension gradually disappeared. Life returned little by little, and after 40 sessions he could be discharged without medication and without pain. His memory and concentration had returned and he could get back to his working life. The treatment was completed 3 years ago and the condition has remained pain free.

Patient No. 5 was a middle-aged woman who slipped and fell on ice in the winter and hit the back of her head. She had a very bad time during the ensuing days. It went better for a short while, but after a few weeks, headaches and neck tension started. This increased over a couple of months and remained unchanged until she presented in the clinic about half a year after the accident. She had been at a pain center where they had put her on treatment with pain medication. In my clinic she was treated with LLLT and massage. It took about 7 sessions before she could feel any improvement, and after approximately 11 treatments, she could discontinue one of 2

painkillers. After approximately 18 treatments, she could stop using the other, and within a few weeks she was completely free from headaches. After 34 sessions, she had fully recovered and was able to go to work again. She was happy and cheerful again. The treatment was completed 2 years ago, and the condition has remained pain free.

All 178 patient records have the same level of documentation and follow-up. LLLT in the hands of an experienced clinician is an effective treatment for myofascial pain.

Discussion

A thorough knowledge of anatomy and pathophysiology is crucial. In practice, this means that one must be medically trained to achieve the best results. To date, there is no agreement on the effect of laser therapy in the literature, but in my experience. amazing results are obtained with this technique. In my clinic, there is thus a 100% success rate with whiplash, tension headache and post-concussion syndrome (N = 178 at the time of writing). Freedom from pain is the dependent variable. In spite of the documentation and the good experience, the treatment has not yet been taken on any payer's agenda in Denmark, so the treatment must be patient-financed, which excludes most people with chronic pain from the treatment. Most of the patients with myofascial pain have quite limited funds to pay with as they live either on sick pay, cash benefits or disability pension (evidenced by my extensive experience with these patient groups).

There are 3 main reasons why public clinics have not taken LLLT on the program. The first and most important is lack of knowledge of the therapy and its effect, which this article attempts to address. The second is the time spent with the individual treatment, typically half an hour, sometimes less, sometimes more. The third is the price of the equipment, which is around DKK 80,000.

LLLT is widespread in the UK, USA and Canada but not yet in the Scandinavian countries. Payment from public or insurance-based payers would allow many more to afford the treatment, thus bringing many back to productive lives that are now unable to work.