

Wieb Patberg 1986 *Brandganzen* Ets 37/50

*Chapter 11*

General discussion



The studies described in this thesis are based on accurate long-term monitoring of several weather and RA variables. All data obtained from 1983 till 2004 are plotted in Figure 1. In the earlier years (1983-1989), the daily joint pain score was the only RA variable that was determined. Although this is a subjective variable, in retrospect it always reflected the pain as it was experienced during the past weeks or months. Since 1989, the ESR was determined regularly in order to have an objective disease variable available. From 1996 on, 2 additional laboratory variables (CRP and RF) were determined more often than before. From March 1999 till February 2003, with intervals of 14 days, the ESR, CRP and RF determinations were alternately done at 2 different laboratories, i.e. about once a month at each laboratory. Although the long-term trend is comparable, the RF curves were at clearly distinct levels (Figure 1, third trace from top). Moreover, the upper curve (lab A, white circles) is very irregular with respect to the lower one (lab B, black and green circles). In general, the ESR and CRP values determined by the two laboratories were comparable. All RF and ESR values used in the study described in *Chapter 8* were determined by laboratory B. Pooling the data from both laboratories would have considerably diminished the correlation of the RF as well as the ESR with the daily time spent outdoors. The ESR values from both laboratories were pooled in the studies described in *Chapters 7, and 9*.

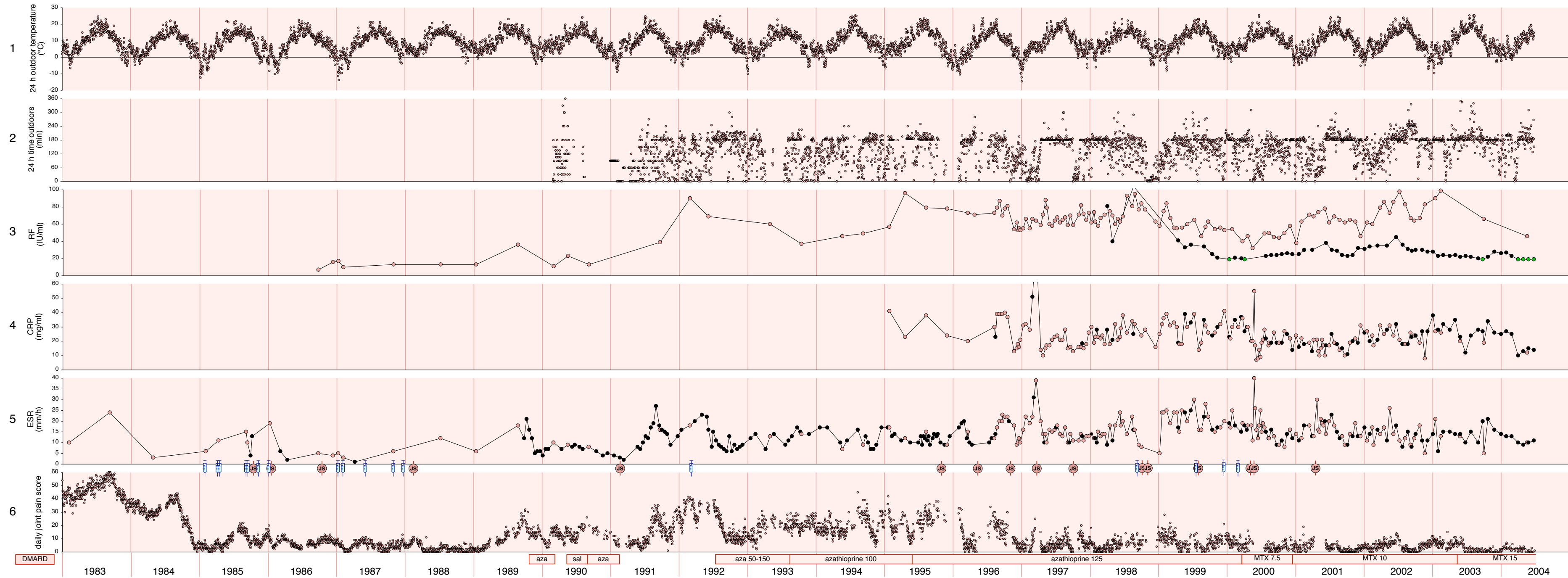
### **Effects of medication**

During the first years of the disease (1979-1991), medication was unstable. The daily dosage of nonsteroidal antiinflammatory drugs (NSAIDs) was dependent on the intensity of pain (cf. Chapter 4, Figure 1). In this way, the variation in pain was reduced, and it was rather the medication that reflected the disease activity than the pain score. From 1992 on, the use of NSAIDs was kept very stable in order to make the daily joint pain score more reliable as an indicator of the disease activity (January 1992-June 2001: 75 mg indomethacin daily; from June 2001 on: 25 mg rofecoxib daily). Probably, due to the stable NSAID dosage the day-to-day fluctuations in pain score after 1992 were higher than before (Figure 1, bottom trace).

From 1992 till 2004, the dosage of disease-modifying antirheumatic drugs (DMARDs) was changed only 6 times (pink bar, Figure 1, bottom). The use of azathioprine did not result in a decrease of the ESR. At a daily dosage of 125 mg, a gradual decrease of the pain score was

Figure 1 **Plot of relevant variables related to the author during 21.5 years (1983 till June 2004)**

<p style="text-align: right;"><i>24 h outdoor temperature</i></p> <p>The temperature was measured by the Royal Dutch Meteorological Institute (KNMI) at the location Groningen Airport. The data are available at <a href="http://www.knmi.nl/product/">http://www.knmi.nl /product/</a>. In the Netherlands, the shape of this curve is almost identical to that of the outdoor vapor pressure curve (cf. Chapter 4, Figure 1). Corrections for stays abroad are given in Chapter 4.</p>	<p><i>Trace 1</i></p>
<p style="text-align: right;"><i>24 h time spent outdoors</i></p> <p>Data represent the total of all periods spent outdoors within 24 h. In general, outdoor activities were light (mostly sitting and cycling) and at temperatures higher than 0-5 °C no coat was worn.</p>	<p><i>Trace 2</i></p>
<p style="text-align: right;"><i>Rheumatoid factor (RF)</i></p> <p>The RF was determined by 2 different laboratories. Due to considerable differences in reported values, the data were plotted in different curves: lab A (pink circles), and lab B (black and green circles). Green circles indicate a value &lt;20 IU/ml.</p>	<p><i>Trace 3</i></p>
<p style="text-align: right;"><i>C-reactive protein (CRP)</i></p> <p>The single high value in 2000 is related to joint surgery. The elevation in 1997 preceded the first joint surgery in that year. Pink circles: lab A; black circles: lab B.</p>	<p><i>Trace 4</i></p>
<p style="text-align: right;"><i>Erythrocyte sedimentation rate (ESR)</i></p> <p>Elevations in 1997 and 2000: as mentioned for CRP. The single high value in 2001 is related to joint surgery. Pink circles: lab A; black circles: lab B.</p>	<p><i>Trace 5</i></p>
<p style="text-align: right;"><i>Joint punctures and surgery</i></p> <p>Syringes indicate puncturing of a joint combined with injection of corticosteroids. Circles marked "JS" indicate days on which joint surgery was performed.</p>	<p><i>Symbols</i></p>
<p style="text-align: right;"><i>Daily joint pain score</i></p> <p>The sum of the pain scores of all 21 (groups of) joints as mentioned in Chapter 1.</p>	<p><i>Trace 6</i></p>
<p style="text-align: right;"><i>Disease-modifying antirheumatic drugs</i></p> <p>aza: azathioprine, sal: sulfasalazine (daily dosages in mg), MTX: methotrexate (weekly dosage in mg).</p>	<p><i>DMARD</i></p>



observed (1996-1999). However, this may also be attributed to the periods with increased time spent outdoors as illustrated by the cross correlation in Figure 2 (black circles). The strong decrease of the pain score as well as the ESR in the summer of 1992 is a nice example of this effect. The transition from azathioprine to methotrexate (MTX) was associated with a decrease of the ESR, CRP, and the pain score, not the RF. Later, in 2001, the CRP increased again, although the MTX dosage was increased. During MTX medication, the ESR showed a light tendency to decrease. However, variations in ESR in this period (2001-June 2004) were clearly related to the daily time spent outdoors ( $r: -0.3; P < 0.05$ ; at a phase shift of 60 days; 2001-2003).

### **"Natural course" of the disease and relationship with season**

In RA, it is difficult to speak of a "natural course" of the disease. The necessary clinical interventions like adjustment of medication, corticosteroid injections into severely inflamed joints, and joint surgery will often disturb such a natural course. Moreover, due to several experiments, the course of the RA variables is far from "natural" (Figure 1). However, in the earlier years (1983-1991) the experiments were limited to a few measures taken to lower the average ambient temperature and vapor pressure during the night, like keeping the bedroom window open and not wearing pyjamas (from September 1984 on; cf. *Chapters 3-5*). The joint pain score, and later the ESR as well, in these early years were in general maximal at the end of the summer, and minimal at the end of the winter (*Chapters 3-6, and 9*). This is reflected in the positive correlation of the pain score with temperature as well as vapor pressure. From 1985 till 1988 there were many clinical interventions, which are likely to have reduced the ESR and the pain score in these years (Figure 1, bottom trace). Joint surgery will have had some lowering effect on the pain score but hardly on the ESR and CRP since the inflammation in the joints involved was mostly burnt out. The main reasons for surgery were reduction of pain, and restoring of lost functions.

### **Effects of daily time spent outdoors**

From 1992 on, the relation of the RA variables with the meteorological weather was often disturbed by outdoor experiments. In general, the RA variables improved in periods when the daily time spent outdoors was long (e.g. June-November 2001), while the opposite was associated with

periods with short daily time outdoors (e.g. November 2001-May 2002). Despite this "disturbance", the relation of the RA variables with temperature and vapor pressure was often discernible. This is described in *Chapter 7*.

The importance of taking the medication into account is illustrated by the clear decrease of the RA variables during a period with short daily time spent outdoors (May-November 2000). Here, the beneficial effect of the transition from azathioprine to MTX prevails over the unfavorable effect of the decreased exposure to the weather.

The disease activity was influenced by the daily time spent outdoors, not the other way round; the time spent outdoors was not increased as a result of feeling better. In fact, the decision to start a new period with high exposure to the weather was often taken in times of increasing disease activity (e.g. May 2002). Since the alleviation during the long outdoors period in the summer of 1992, I considered being outdoors as an essential part of my therapy. Further, cross correlation revealed that the changes in RA variables lagged behind changes in time spent outdoors. In Figure 2, this is illustrated for the RA variables ESR and joint pain score (1997-2003). As in the study described in *Chapter 9*, the correlogram gives the impression that changes in ESR precede changes in joint pain score. Note that other measures for the reduction of the 24 h ambient temperature and humidity were in effect as well: not wearing pyjamas and keeping the bedroom window open (since 1984), and not wearing a coat outdoors at temperatures above 0 °C (since 1992).

In a study like this, research and therapy go hand in hand. A rigid experimental protocol will give clear and quick results but may lead to worsening of the patient's situation. For instance, staying indoors for a long period might show a clear increase in ESR, CRP, and RF values, along with an increase in pain. Scientifically, this would be a valuable observation but ethically it is not acceptable. However, the lack of effects of long-lasting periods with daily very short time spent outdoors is somewhat compensated by the effects found during a few short periods in which the patient hardly was outdoors (January-April 1997, October-November 1997, and November 1998-January 1999). In all these periods there was a clear increase in joint pain score, ESR, CRP, and RF. As shown in Figure 1, medication was stable during all these periods.

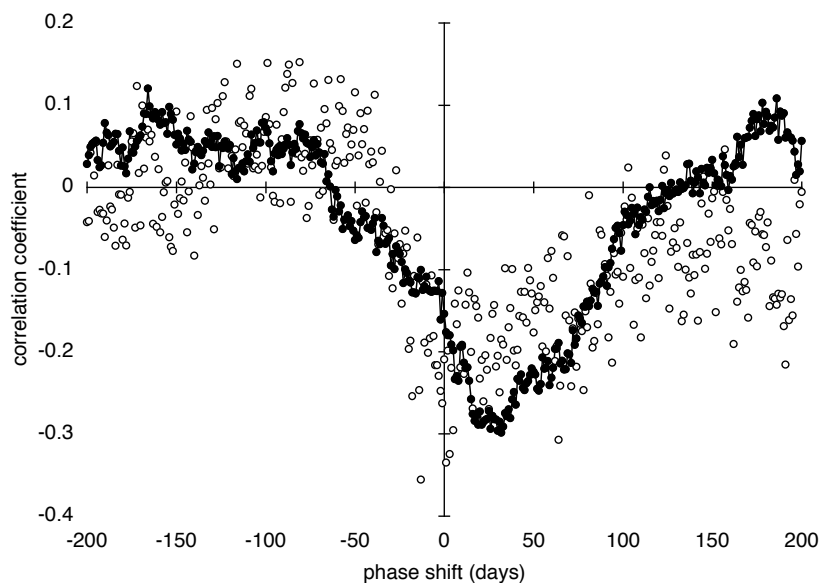


Figure 2 Cross correlation of the ESR (○) as well as daily joint pain score (●) with the daily time spent outdoors during 7 years (1997-2003). The minimum in correlation coefficient was -0.30 ( $P < 0.01$ ) for the correlation between time outdoors and the pain score at a phase shift of 32 days. This indicates that changes in time spent outdoors are about 1 month later followed by opposite changes in pain score. The changes in ESR seem to be less delayed, although the minimum in correlation coefficient is not very clear.

### Microclimate

The results of many studies on effects of the weather on RA can be explained best by assuming a positive relationship between RA variables and the humidity of the microclimate close to the patient's skin. This is the conclusion of the review described in *Chapter 2*. In addition to the outdoor humidity, the humidity of the microclimate is influenced by housing, clothing, air conditioning, etc. This is illustrated in Figure 3. In general, the indoor humidity is higher than outdoors due to several sources of water vapor, like cooking, bathing, respiration, especially when ventilation is poor (Figure 3, filled circles). The humidity of the microclimate is still higher due to water evaporation through the skin even if no sweating occurs.

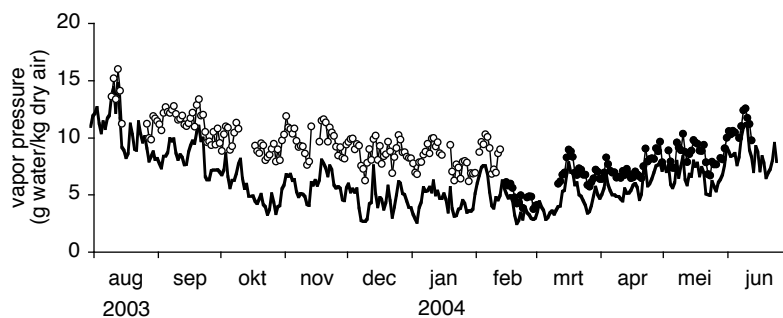


Figure 3 Course of the 24 h mean vapor pressure measured outdoors (solid line), in the ambient air on the clothes (filled circles), and in the microclimate at the skin (open circles) of the author living at Groningen, The Netherlands. Outdoor vapor pressures were calculated from the outdoor temperature and relative humidity data supplied by the Royal Dutch Meteorological Institute (KNMI) for the location Groningen Airport. Temperature and relative humidity data for the calculation of the vapor pressure of the ambient air and the microclimate were obtained using a data logger (Gemini Data Loggers, Tiny Tag Ultra TGU-1500; 10 minutes measuring interval). From August 2003 till February 2004, the data logger was worn on the skin of the chest as a necklace (at night fixed to the quilt cover facing the skin), and from February till June 2004 attached to the belt (at night fixed on top of the quilt cover).

The difference in humidity between the microclimate and the air outdoors is very small in August (light clothing, open windows, more living outdoors) and it increases in the colder months (Figure 3, open circles). The increase of the humidity of the microclimate, caused by more clothing is considerable (Figure 3, compare open and filled circles in February 2004). Note that in the cold months, the humidity of the microclimate is almost twice as high as the outdoor humidity. These data support the conclusions of the above-mentioned review (Patberg & Rasker, 2004). It is remarkable that the correlation of the daily joint pain score with the vapor pressure of the microclimate is stronger ( $r: 0.25$ ,  $P < 0.05$ ) than that with the outdoor vapor pressure ( $r: 0.17$ ) (Figure 4, cf. correlation coefficients at phase shift 1 day). This supports the hypothesis that the humidity of the microclimate influences the disease activity.

Initially, the purpose of spending more time outdoors was to reduce the mean temperature and humidity of the ambient air. Having found subsequent beneficial effects on my disease, I became more convinced that there is a relationship between the daily means of these variables and the variables of my RA. Later, I realized that staying outdoors for e.g. 3

hours, in which the vapor pressure of the microclimate is reduced e.g. from 8 to 4 g water/kg dry air, will decrease the 24 h mean vapor pressure of the microclimate from 8 to only 7.5 g water/kg dry air. This change is negligible with respect to the fluctuations shown in Figure 3. The same reasoning is applicable for the temperature of the microclimate. Therefore, I consider the actual situation during the stay outdoors, with strong decreased vapor pressure and temperature, to have an effect, not the change in the 24 h mean values.

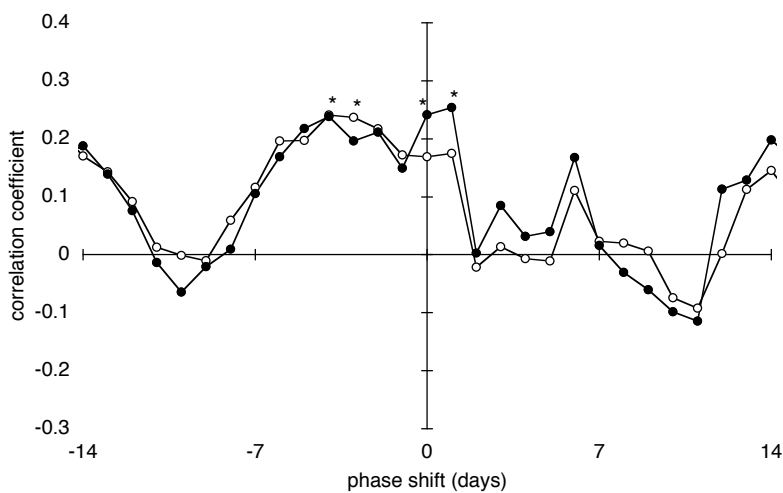


Figure 4 Cross correlation of the daily joint pain score with the outdoor vapor pressure (○), and the vapor pressure of the microclimate (●) (August 2003-February 2004). On days when the mean vapor pressure of the microclimate was not available, the corresponding data of the outdoor vapor pressure were discarded in order to keep the correlograms comparable. At a phase shift of +1 day (vapor pressure preceding the pain score) the correlation coefficient of the relation of the pain score with the vapor pressure of the microclimate is clearly higher than the relation with the outdoor vapor pressure (\*:  $P < 0.05$ ).

As mentioned, about half the time spent outdoors, I was cycling, mostly without a coat. Therefore, it might be argued that the exercise, rather than the weather has caused the beneficial effect. However, observations in the summers of 1995 and 1997 refute this: the disease activity (Figure 1: CRP, ESR, and joint pain score) did increase with increasing temperature and vapor pressure although about 3 hours were spent outdoors daily. Not until the decrease in temperature and vapor pressure at the end of the summer (1997), the disease activity decreased.

### One subject

Except those described in *Chapters 2, and 6*, the studies were all done on one and the same patient. Therefore, this thesis should be considered as a report of a comprehensive pilot study. In order to answer the question “How common are beneficial effects of being outdoors in RA patients?” plans are made to repeat the study done on myself, on 30 other patients with RA. There are several reasons to assume that the reported results do not belong to a unique case:

- The effect of the weather on the daily joint pain score of myself is comparable with that on the daily mean score of 88 RA patients in an earlier study (*Chapter 6*).
- In personal reactions on publications of my studies, many RA patients declared that they had experiences similar to those I had reported.
- The most recent review of the literature on weather effects on RA concluded that there is a relationship between RA complaints and the humidity of the microclimate at the patient’s skin (*Chapter 2*). Hence, the increased ventilation of the microclimate when staying outdoors may be expected to be beneficial to other RA patients as well.
- Even the statement of RA patients that they feel better on holidays in a warm country is in accordance with my own experiences. Although the temperature and vapor pressure are rather high, people will be outdoors almost all day, and wear only few clothes. Therefore, the vapor pressure at the skin will not build up.

### Conclusions

The primary aim of the studies in this thesis was to explore whether the variations in the disease activity of my own RA were related to “whatever”, and if so, whether it is possible to manipulate that “whatever” in order to suppress the disease activity as much as possible. Probably, there are several “whatevers” influencing the disease, but one of these is associated with the temperature/humidity complex of the microclimate. There are many possibilities to manipulate this complex, i.e. making the microclimate cooler and less humid, which after some delay, turned out to decrease the disease activity. The effect is reversible, so for a prolonged beneficial effect, the manipulation of the microclimate needs to become a daily routine. Due to this reversibility it is possible that the objective RA variables ESR, and CRP in general did not significantly decrease. The slightly lower level of these variables since 2000 (Figure 1)

should be attributed rather to the medication than to being outdoors. However, the relation between being outdoors and the RF is significant, and the gradual decrease of the RF since spring 2002 is likely to be associated with the, in general, long time that was spent outdoors daily. Several factors may have caused the low level of the joint pain score in the later years: the medication, joint surgery, and even psychological factors. In addition to this, the many hours that I have spent outdoors have had a favorable influence on the pain score as has been illustrated above (Figure 2).

### **Underlying mechanism**

The underlying mechanism is unknown. The words of the British physician, and discoverer of argon, John W. Strutt (Baron Raleigh, 1842-1919) nicely express how hard it is to imagine that changes in humidity of the air can have effect on the human body: “I cannot conceive why we who are composed of over 90% water should suffer from rheumatism with a slight rise in the humidity of the atmosphere”.

Perhaps, evaporation by the skin plays a role; this will increase when the microclimate becomes less humid. It is possible that spending more time outdoors, which is more or less experienced as physical stress, stimulates the production of cortisol with subsequent suppression of inflammation in the joints. The use of alcohol would inhibit this influence by its lowering effect on the production of cortisol (*Chapter 10*). In a future study it would be interesting to investigate whether a period in which 3 hours are spent outdoors daily, will increase the cortisol level.

### **Future research**

Suggestions for further investigations on the relationship between the microclimate and RA variables are given in *Chapter 2*. Of course the next question to be answered is “How common are the beneficial effects of being outdoors in RA patients?” The results found on myself justify a study on other patients with RA. Depending on the results of the above-mentioned project on 30 patients, measures taken to decrease the humidity of the microclimate might become advisable for patients with RA.