



oration

Dr. Marjolein Drent

'Breathtaking inspirations...'

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'Water is the wizard'

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'Breathtaking inspirations ...'

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Oration

held when accepting the office of
special professor of lung diseases, especially
'interstitial lung diseases', at the University of Maastricht

on Friday 12 May 2006

by

Dr Marjolein Drent



University Maastricht



‘Breathtaking inspirations ...’

Rector Magnificus, board of the university, respected colleague professors, colleagues from the Netherlands and abroad, staff of the azM, patients, family and friends and all others present...

Today I shall officially accept the position of Professor. I regard it as a great honour and an enormous privilege that I am able to speak my inaugural address in front of you. In this address I shall try to give you a breathtaking introduction to the subject of my inspiring study ‘interstitial lung diseases’ and the social and scientific importance of this chair. Cooperation with a variety of disciplines, many of them represented here today, is essential in this context. The approach is very similar to that of a detective: meticulously sifting and searching for occasionally unexpected links.

Contact organ

First of all I would like to talk about the concept of a contact organ and the relationship between a contact organ and the development of diseases. The most obvious and best-known contact organ is our skin. All kinds of substances can penetrate the body through the skin and sometimes they have an undesirable effect. However it is not the skin but the lungs that form our largest contact organ. The surface of the skin is about $1\frac{1}{2}$ m². The surface of the lungs is about 90m², in other words half the size of a tennis court. The surface of someone’s lungs is therefore about 60 times greater than the surface of their skin.

You could therefore say that the lung is ‘embedded’ in two environments, both of which can introduce harmful substances. First of all there is a variety of contacts with the surrounding air. The function of the lungs is to exchange gases: we inhale air containing oxygen (O₂), which is absorbed, and carbon dioxide (CO₂) is then exhaled.

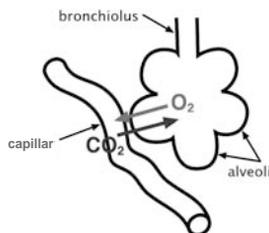


Figure 1 – Gas exchange in the lung.

This gas exchange takes place in the lung air sacs (alveoli). In this way blood low in oxygen returning from the body becomes rich in oxygen again (figure 1). Contact via the lungs is less direct, but cannot easily be impeded. The air that someone inhales can literally be breathtaking if it contains harmful organic or inorganic particles or gases.

In addition, the lung is in close contact with the blood supply. Along this route, it is also possible for a variety of harmful substances to reach the lung and literally take your breath away. This will be the main gist of my story this afternoon, alongside the importance of multi-disciplinary cooperation.

Interstitial lung diseases

Most common lung diseases are disorders that make it difficult for people to get enough 'air', making them feel breathless. In this case there is a problem with the paths that provide access to the lung (the branches of the tree), as in the case of asthma and COPD (emphysema). In addition, problems can arise as a result of inhaling air containing particles and/or gases. Inhaling certain substances starts up an immune or protective mechanism. This defence process usually passes without major problems and the person in question does not fall ill. For people who are overly sensitive, this process gets out of hand, the immune reaction is too fierce and results in a lung disorder. In the case of these diseases, the lung tissue itself is mainly affected. These disorders are called interstitial or diffuse lung diseases. In the Netherlands an estimated 20,000 people suffer from one or another form of such diffuse lung diseases.

Damaging influences from without

In the Province of Limburg, diffuse lung diseases due to inhalation contacts are not unknown. Everyone has heard of the 'black lungs' or 'brown lung disease' of miners. These workers inhaled coal dust into the lungs. Coal dust contains silica, an inorganic material. The lungs have a natural cleaning function. This is made up of an army of vacuum-cleaner cells that try to clean up all the dust particles. In order to do this, they have to break down or digest these particles. That is the problem, you see: they can't. The cells die and the next generation tries the same. These cells are also unable to do the job. Substances harmful to the lungs are released during this process. At a certain point, the lungs start to display noticeable abnormalities. It becomes increasingly difficult to breathe, to take in oxygen. Stamina declines and a chronic cough can result. This disease is not restricted to the miners themselves. It is also found in members of a household who, for instance, wash the miner's clothes. Other job-related sufferers include sandblasters, workers in the glass and rubber industries etc.

Cause and effect

I soon became interested in questions such as: why are certain substances harmful to one person but not to another? What is the basis of certain abnormalities seen among patients? What is the cause? Occasionally the result of extensive research is inadequate and we get no further than sticking on the label 'idiopathic', in other words – cause unknown.

Factors that influence the development of a disease

- exposure
- circumstances
- sensitivity or hereditary disposition
- or a combination of all of these?

In order to decide on the most suitable treatment for a patient, it is necessary to find out the possible cause of the resulting abnormality. Could it be that person's exposure to a harmful substance? Does it involve an innate tendency to develop a certain reaction or a combination of exposure and sensitivity? Why is a specific substance harmful to a certain person? What decides whether someone will eventually develop an illness? At first sight these may seem like fairly simple questions, but it isn't easy to provide a proper answer to them.

Correct information

First of all, the patient's story is very important. In order to find out what is wrong with someone, and above all how a certain disorder can develop, it is of essential importance to acquire adequate information about all the things someone has done. You cannot make do with a brief case history, an extensive inventory of possible contacts and exposure to them is necessary. The doctor has to be persistent and dogged.

Asking the right questions and being a good listener can help to unravel the puzzle. In practice, this quite often suffers from lack of time, which can curtail the perseverance and forbearance of the caregiver. The right dose of curiosity is essential, bearing in mind the fact that the potential cause of diffuse lung diseases may be any particles or substances that have been present in the air inhaled or in the blood (figure 2).

Creativity is a precondition to identifying possible 'triggers' with the patient. The approach is comparable with that of a detective. Sherlock Holmes made use of what is known as the deduction method. I shall now examine that under the magnifying glass with you.

Close cooperation between various disciplines and a combination of expertise is very important. An additional advantage of this is that the expertise can be extended further and further, that links can be made which can lead to

the initiation of new scientific research. In addition, the care of patients with such diseases can be improved. Within the azM, all kinds of initiatives, including azMove, are used to encourage people to abandon the island culture and strive for the greatest possible degree of virtual cooperation.



Figure 2 – *This man has celebrated carnival in a breathtaking way. Unfortunately for him it ended with the development of what is called 'confetti lung'. We see this diffuse interstitial lung disease quite often among people whose hobby is excessive partying. ☺*

The right diagnosis

The primary aim of a treatment is to improve the patient's quality of life. In order to achieve this as well as possible, it is first of all essential to make the right diagnosis. There are several reasons for this.

Approaching patients' problems

1. a good interviewer who asks the right questions and makes an inventory of all possible substances with which there has been contact and all medicines used
2. clinical investigation:
 - laboratory tests
 - visual techniques
 - . radiology
 - . nuclear medicine
 - microbiology
 - pathology
 - the right appointments based on indications
3. additional specific techniques
 - electron microscope (EM) analysis
 - DNA investigation, polymorphisms
4. provocation

In addition, it is essential to look for possible causes and genetic elements. For scientific research including genetic research, it is necessary to ensure effective clinical demarcation.

The importance of the right diagnosis

- significant for the prognosis
- what does the patient have in store?
- trying to avoid contact with possible triggers
- prevention management
- a timely start of optimal treatment

A clear definition of the so-called phenotype (the clinical presentation) is important in order to be able to draw any conclusions about the genotype (genetic makeup) with the aid of DNA research.



Figure 3 – *Sherlock Holmes, consultant detective, famous for his powers of deduction.*

Cooperation

Multidisciplinary, multicentric, national and international cooperation in caring for patients with interstitial lung diseases can ensure that much is achieved. This is also clear from the results of research that has partly come about through cooperation with other institutions and groups.

In this context, it is therefore most welcome that the basis has been laid in Utrecht to take the field of interstitial lung diseases seriously. Recently the years of experience in this field of my mentor and model Professor J.M.M. van den Bosch working at St Anthony Hospital in Nieuwegein have been crowned with a chair.

I am delighted that we have expressed the intention of joining forces to work to tackle interstitial lung diseases in the broadest sense. The aim will be to acquire an important position in the Netherlands with regard to scientific research and patient care.

Cooperation

- general practitioners
- clinicians
- paramedics
- basic scientists
- company doctors
- patient societies
- health insurance companies
- industry

In order to improve the quality of life, it is very important to find the best treatment, but possibly even more important for the future is to set up measures to ensure adequate prevention. Here too cooperation between clinicians, scientists, industrial medical officers, health insurers, patient associations and also industry are of essential importance. These latter partners could also be encouraged even more to invest in creating the best possible working climate for their employees. Attention should also be focused on the occasionally invisible risks for the consumers and handlers of their products. Good information is of great importance. Cooperation can lead to the formulation of national and international guidelines and improvements in prevention and management. The best possible use can be made of the latest scientific developments, such as DNA research and advanced investigation of contacts. With the knowledge acquired, the best possible individual treatment can then be decided on. This knowledge can also be used to set up international networks to prevent and combat bio-terrorism.

Causes of interstitial lung diseases

The term interstitial lung diseases is fairly complex and needs clarification (figure 4). Diffuse lung diseases can develop as a result of contact with organic material.

After inhaling proteins or fungi, some people can display a kind of allergic reaction, which can in turn lead to lung disorders. A well-known example of such a disorder is what is called 'Pigeon Breeder's Disease'. Proteins in the birds' faeces cause the problem. The faeces can be among the birds' feathers, but also in feather duvets, pillows and even among the feathers of stuffed birds.

Fungi and a variety of drugs can cause a similar reaction. I would like to use several examples to illustrate the fact that it is not always easy to trace such a cause.



Figure 4 - *ild: 'I love ducklings'.*

Sherlock Holmes: 'The Mystery of the Pigeon Breeder's Dog'

The first example is of a boy aged nine with what is known as 'pigeon breeder's disease'. His father is a professional pigeon breeder. His parents assured me that he no longer had any contact whatsoever with the pigeons and never entered their cages. When I spoke to the boy about the situation at home, he told me they have a dog. He loves the dog and often plays with it. The dog did go into the pigeon cages and regularly lay there in the sun. The dog's fur harboured faeces from the pigeons. The boy regularly stroked and cuddled the dog and so he still had indirect contact with the pigeons. He was not allergic to the dog, but in this case the dog was the vector for proteins harmful to the boy.

Sherlock Holmes: 'The Case of the Breathtaking Wine'

Another example concerns a notary who had just gone into retirement. Recently he had become increasingly breathless and turned out to have a low oxygen level in his blood. An x-ray and a high-resolution scan (HRCT) of the lungs showed diffuse defects (figure 5).

In order to find out the cause of these defects, he was given a bronchoalveolar lavage (BAL). This indicated that the image on the x-ray most closely fitted an allergic reaction caused by contact with birds or fungi, for instance.

The patient's wife was asked about any possible connection with something in the home. We were unable to find any explanation. In the end an assistant made a very extensive inventory of everything the patient did every day.

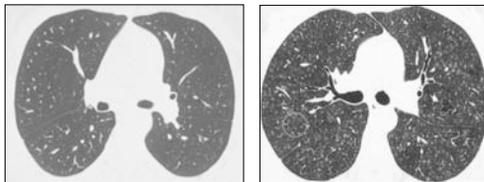


Figure 5 – A high-resolution CT image (HRCT). On the left are normal lungs, on the right the patient's lungs. Here you can clearly see these so-called diffuse defects (medical term: 'extrinsic allergic alveolitis').

At that point the patient said that every day he went to fetch a bottle of wine from the cellar for dinner.

This cellar turned out to house the cause of the problem (figure 6). In this case it is a question of 'breathtaking wine'. These are but two examples from a long list of interesting and striking observations, many of which you can find in the literature.



Figure 6 – Picture of the cellar wall covered with fungi.

Scientific effects of an observation

Inhaling inorganic material, such as the coal dust mentioned before, fine dust, but also metals, aluminium, beryllium and insulation materials such as rock wool and glass fibre can lead to harmful reactions in the lung.

Sherlock Holmes: 'The Mystery of the Fibres'

Once it is clear that someone with a lung disorder has been exposed to insulation materials such as glass fibre or rock wool, this evokes the following questions. 'Did it make the person ill? How is it possible to show with an acceptable degree of probability that there is a link?' After all, his colleagues did not fall ill. Is it because the colleagues have taken better protective

measures or does the person in question apparently react in a different way? Does he have an overactive immune system that makes him ill?

In order to answer these questions adequately, it is first necessary to demonstrate that rock wool or glass fibre really did enter the lungs. In order to do this, a biopsy (a piece of lung tissue) is examined using electron microscopy and element analysis.

Qualitative microanalysis shows a number of peaks of elements present (see figure 7a): magnesium, aluminium and silica. These same peaks are present in figure 7b, but now much sharper, because this is original rock wool material. Figure 7c shows a scan of a piece of lung tissue without fibres where the peaks of these elements are absent.

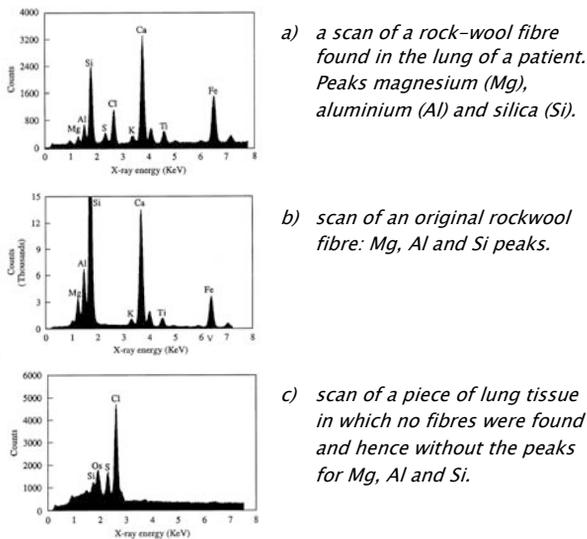


Figure 7 – Element analysis (*Respir Med* 2000,94;815–20)

Scientific foundation

The next step is to try and show that the sick person reacts differently to contact with rock wool or glass fibre from other employees who are not sick. In other words: does the sick employee stand out in any way? Is there a genetic difference?

Alongside genetic testing, with the aid of DNA, we can also carry out provocation tests. If we expose blood from a test subject or a patient to a particular substance, for instance glass fibre, and measure the strength of the reaction to this exposure, we can determine whether the reaction is stronger

than or different from that of a healthy individual. In this way an observation in practice – namely the exposure to a particular substance – becomes a hypothesis and test methods are developed to check this assumption.

In order to embark on this route, good cooperation between clinicians and scientists is essential. In addition it can also be stimulating when scientists know why they develop a particular test and when clinicians in turn are aware of the possibilities. This might seem obvious, but it can be encouraged much more and forms a significant part of what is called translational medicine.

Educational function

When a specific case is solved, it is important to work out the story and write it down in the form of a case report and then to offer this to a scientific journal. In this way, other colleagues can become aware of this striking observation and this can in turn motivate them to think about the possibilities. The clinical impact of such an example can be enormous but this does not 'score' in a scientific sense. Indeed, these days the powers-that-be advise young researchers and doctors not to write out and report such observations. The reason given for this advice is generally that the impact factor is too low. In this way, young and enthusiastic doctors and researchers are denied a unique opportunity to become acquainted with the meticulous recording and reporting of a significant observation. This experience could also awaken interest in carrying out scientific research. In addition, this discouragement displays a disregard of the value of clinical observations.

The present evaluation system of significant clinical observations on the one hand and research results on the other is in need of critical examination. This situation is comparable with the sports world. If the crossbar is put up too high from the start, you deny sportsmen and sportswomen the motivation to develop into top ranking players. In order to deliver a great performance, you need talent but you also need a good coach, one who protects you from overexertion. The right training schedule is crucial.

Social relevance

We still face the effects of exposure to asbestos. In the past many people, knowingly or not, came into contact with this insulation material. As a result of all kinds of protective measures taken, direct exposure is at present virtually nil. Yet doctors will still often be confronted with diffuse or other lung diseases in which exposure in the past may well have played a role.

If it is determined that a relationship between the disease and exposure is possible, then the provision of good information is very important. There has to be good cooperation between industrial medical officers, medical examiners and general practitioners. In addition the producers and customers of these products play a significant role. If these parties are regarded as partners in

research and are also willing to invest in it, then both industry and health care can profit. Bringing together knowledge, generating financial means and developing the right preventive measures also demands close cooperation. For instance industry can play an important role in innovative developments within health care. These developments can additionally lead to better working conditions for employees and improve prevention management (figure 8).



Figure 8 – *Protective suits are necessary in some trades to protect employee bronchial tubes.*

Sarcoidosis

Another disorder for which I would like to ask for your attention is sarcoidosis. This is a fickle disorder. The cause is still not known. A great deal of research has been carried out, but there is still a lot that needs to be found out. It is a disease that can affect virtually any organ. It can be found throughout the world in any race. There are differences in its severity and its course. Its course is often more serious among people of African descent. In the Netherlands, about 7000 people suffer from sarcoidosis. Good epidemiological research is however still lacking. In order to treat people well when they have a disorder such as sarcoidosis, it is important to know what its consequences are for those involved. What is the impact on the quality of life? What do these people need help with? It is important that those treating them are well informed about the problems their patients are faced with. This can lead to more understanding and better treatment advice.

In Maastricht, the Sarcoidosis Management Team was founded in 2000. The team is made up of representatives from various disciplines. Offering the best

possible care and the right care for sarcoidosis patients remains the most important aim of this cooperation within the azM. In the ild care centre that is being set up, this fertile cooperation will be used for patients with systemic disorders and other interstitial lung diseases.

Sherlock Holmes: 'The Case of the Killing Fatigue'

Research carried out by Ruth Wirnsberger in cooperation with the *Sarcoïdose Belangenvereniging Nederland* (Dutch Sarcoidosis Association) revealed what we already knew from the stories of the patients, namely that fatigue has an enormous impact on the life of sarcoidosis patients. This is not the kind of fatigue that we all know when we have been too busy, have gone to bed too late, made too many appointments, subjected ourselves to jetlag etc. This is an all-consuming fatigue that can have so much influence on someone's life that normal functioning is no longer possible and everyday activities are too difficult. Creativity is curbed, imagination checked and talent restrained. It ensures personal dramas and can cause great social and financial problems.

My first 'scientific publication' was a response to an article by Professor van Rood about the influence of stress on immunity and the great importance of multidisciplinary research. This looked at the major influence of all kinds of stimuli on the functioning of the immune system. Later I was to be confronted with the influence and impact of this for sarcoidosis patients. An all-consuming fatigue can be the effect of an overactive and overworked immune system.

Observation in practice: fatigue

Fatigue is a vague concept. How do you determine whether someone is tired or not? How can you decide what the influence of fatigue is on whether one can function or not?

There is as yet no good yardstick to measure fatigue. This has not been made possible with lung-function, blood or other tests. A concomitant problem is that the patients do not usually look sick and are often not taken seriously by the people around them and their employers. Fatigue is something vague, something intangible and there is so far no good 'fatigue' meter (figure 9).

For people with sarcoidosis, it is very important to find an explanation for fatigue and to develop a reliable yardstick to measure it with. In the case of medical examinations, it is important to find deviant figures that can be compared with normal values. Our future research will be focused on this.

Observation in practice: vague complaints

In the case of sarcoidosis, many substances secreted from granulomas, in other words aggregates of immune cells, cause inflammatory reactions in the body. These substances can lead to a reduction in muscle function. Stamina is

reduced considerably and a variety of vague complaints can result, such as pain and restless legs. Occasionally eating disorders are seen. Patients attending outpatients' clinics repeatedly mention these vague complaints. This turned out not to be coincidental; a pattern was certainly emerging. Consultation with the neurologists at first provided no leads, but eventually several patients came to Elske Hoitsma. She recognised the pattern of complaints that matched a small-fibre neuropathy.



Figure 9 – *The Fatigu-o-meter provides a measure of how much energy reserve someone has.*

The nervous system has a variety of guidance systems. The thick or voluntary fibres are responsible for movement. The so-called small or involuntary nerve fibres are involved in experiencing pain, feeling temperature and regulating blood pressure. When a disorder emerges here it is called an autonomous dysfunction. This latter fact partly explains the fairly vague complaints including fatigue. Not satisfied with a standard answer and willing to deviate from the norm, Elske Hoitsma, together with patients and members of the Sarcoidosis Management Team, was able to make a discovery that turned out to have a major clinical and scientific impact, as can be seen from the interest it awoke in the international scientific world. This observation partly came about thanks to close cooperation between the departments of lung diseases, neurology and clinical neurophysiology.

Scientific foundation

There is a very active international network. Dr D.G. James took the initiative to found the WASOG. This international organisation concentrates on collecting information and informing colleagues about sarcoidosis and related disorders, compiling guidelines, organising world congresses. It also publishes a meritorious journal.

In 1958, Dr D.G. James organised the first international congress on sarcoidosis in London. He gave me a challenging scientific commission, namely to find the cause of sarcoidosis (figure 10).

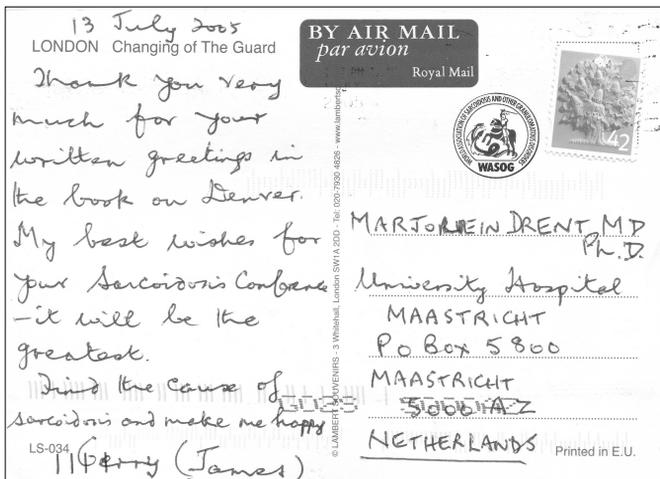


Figure 10 – Scientific commission from Dr D.G. James, founder of WASOG.

Our own investigations put us on the track of the fact that the autonomous or involuntary nervous system of sarcoidosis patients and other patients with disorders affecting the immune system is regularly affected. This helps to explain the vague complaints. This again finds its basis in the inflammation or inflammatory reaction that takes place in sarcoidosis and other disorders of the immune system. This finding provides a fresh impulse for research into discovering effective treatments.

Social impact

This observation is of major social importance in view of the fact that sarcoidosis is generally seen among relatively young people. Unfortunately this illness often leads to a long and undesirable period of sick leave. When a patient then reports to the medical examiner that he or she is tired, too tired to

work, the answer is generally 'we all get tired sometimes'. In other words they often face misunderstanding and have to defend themselves at all times. This is not only annoying but such stress certainly does not contribute to recovery (figure 11). Understanding of a patient's surroundings and above all recognition of the problem is very important for the healing process. In addition it is important that patients themselves learn to cope with being ill and learn to accept its limitations. You see, it is not always possible to treat the disorder adequately.



Figure 11 – *The problem of this age: stress at work. Recent research even indicates that 'sick building syndrome' is not caused by a 'sick' building, but by stress and the pressure of work. (Occup Environ Med 2006; 63: 283–9).*

Breathtaking drugs

After discussing several external causes with breathtaking consequences, I would now like to look at possibly harmful effects of substances that reach the lungs from the inside via the blood supply.

As doctors, we have many drugs at our disposal. Often patients have more than one disorder, as a result of which several drugs are taken together. Alongside the intended effect, drugs also have side effects. Sometimes they cancel each other out; in other cases they can strengthen each other's effects. The Formulary and the patient information leaflets are full of these.

In the field of lung diseases, we are also familiar with drug-induced toxic lung reactions. In this case, there is a reaction in the lung tissue (lung parenchyma), making it more difficult to absorb oxygen. In its presentation, this looks very much like the examples I just discussed. Drugs can also have breathtaking consequences. The number of drugs that can have harmful effects on the lungs is growing daily. The reason for this is primarily that people are

now more alert about making the link. In this case it is of the utmost importance that unusual observations should be described and reported in order to inform others of possible side effects which have not previously been observed.

Side effects of drugs in a broader perspective

Every day, about 10 people die in the Netherlands as a result of side effects of drugs and half of these cases could be avoided. This is clear from an investigation carried out by the VARA/NPS TV news programme Zembra and broadcast last year. Every year, about 3500 to 4000 people die as a result of side effects of all kinds of drugs. Much is done to evaluate possible side effects of a drug before it is approved for use. However, little research is carried out into the possible effects of the use of several drugs at a time.

Pharmaceutical companies primarily investigate the side effects of the products they themselves supply. There is not enough consideration for the fact that patients often have more than one disorder and hence also use several different drugs. These drugs can influence each other and eventually cause a toxic effect in the patient. In deciding whether their product is safe for a patient, in the future more attention should be focused on the effect of using combinations of substances. Close cooperation between doctors and pharmacists is very important. The pharmaceutical industry could also take this to heart and consider paying more attention to cooperation than competing with each other with often similar products. This could also free up financial resources and lead to a restructuring of development strategies.

Scientific foundation

Why does one person react to certain stimuli or to a certain drug or a combination of drugs with a toxic reaction in the lung or elsewhere and someone else doesn't? What causes this? Is it possible to predict whether someone risks displaying a toxic reaction? But, possibly even more important, can this reaction be prevented?

In order to understand why a certain drug can be harmful, it is important to know its composition and how it is broken down in the body. Some drugs are transported out of the body by the kidneys (efficiently working kidneys are essential). Specific enzymes in the liver break down other drugs.

These enzymes include what are known as the cytochrome P450 (CYP 450) enzymes. These enzymes are capable of breaking down drugs instantly. In the case of most people, drugs break down without any problems arising. For some people however, the system works a little more slowly, as a result of which the drug takes longer to break down. If this is the case, you could prevent problems by lengthening the time between doses. There are also people whose

systems quickly become overloaded. In that case, it might be a hereditary defect, for instance a CYP450 polymorphism.

We can investigate this with the aid of genetic material: DNA. In order to explain why one person falls ill after contact with a certain substance and another one doesn't, one can for instance look for the presence of polymorphisms. In the Netherlands, an estimated 20% of people suffer from one kind or another of such a polymorphism and a higher risk of anomalies.

Sherlock Holmes: 'The Mystery of Human DNA'

You can imagine human DNA as a book. This book has 23 chapters (figure 12).

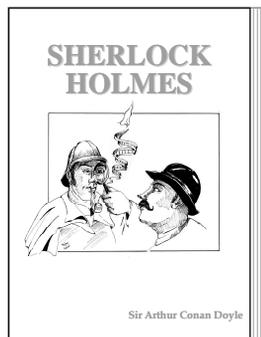


Figure 12 – *The Mystery of Human DNA*.

A gene can be compared with a paragraph. A gene codes for one protein, in other words describes the composition of one protein. A mutation or polymorphism arises when one word is written incorrectly or is absent or added.

A point mutation comes about when one letter is absent or another letter replaces it. The appearance is no longer as intended and the meaning of the word is no longer clear. I'm sure you all know the problems that can arise if you make a typing error in an e-mail address. You are made aware of this at once because the server immediately replies that the e-mail cannot be delivered!

Monitoring in Practice

If someone has a defect in the system that breaks down certain drugs this causes a greatly increased risk of developing harmful side-effects. In this case, prescribing such drugs is to be avoided (figure 13). In practice however little use is made of this, strangely enough.

In 1993 the Netherlands Tijdschrift voor Geneeskunde (Netherlands JMS published an article entitled: '*Psychische klachten door een overdosering van theofylline; noodzakelijkheid van spiegelcontrole.*' (Psychiatric complaints as a

result of an overdose of theophylline; the necessity of checking the blood concentration.) This article describes two patients both of whom clearly displayed very severe theophylline intoxication with serious clinical results. This served to stress yet again the importance of careful dosing of theophylline bearing in mind several factors that influence the serum concentration and regular checks of that serum concentration. Determining the concentration is necessary because of major individual differences in pharmacokinetics, the small margin between the toxic and therapeutic concentration and the severe side effects. The metabolism of theophylline is partly dependent on cytochrome P450 enzymes. A sharp reduction of chiefly arterial liver flow, as can take place in the case of heart failure resulting in liver ischemia, also results in a reduction of the activity of the cytochrome P450 system. In addition, in administering a combination of drugs, different effects can take place than when administering each substance on its own. In 1993, we did not yet have a technique to show whether there might be a problem with the breakdown of theophylline in these patients.

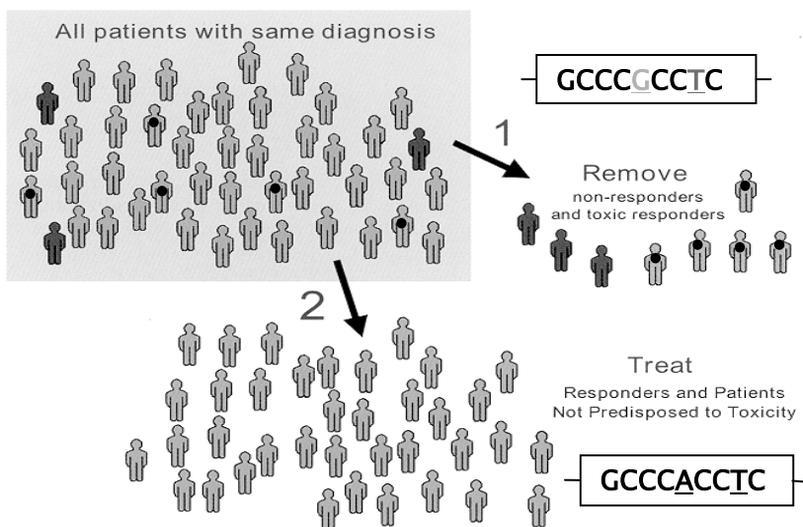


Figure 13 – *Pharmacogenomic knowledge applied in medical practice. It is important to be able to distinguish people who react in the desired way to a specific drug from those who have a toxic reaction or do not react at all (Ann Rev Pharmacol Toxicol 2001;41:101–21).*

I continue to be fascinated by the question: 'how can it be that one person displays a toxic and harmful reaction after taking a specific drug, while a large group reacts in a normal and desirable way and another group reveals little or no effect?'

We now know more about the influence of sensitivity in dealing with drugs and especially the possible development of side effects.

Perspective for the Future

By determining in advance whether the body's ability to break down drugs is functioning the full 100 per cent or not, a great deal of suffering can be prevented. With this knowledge, the right dosage advice can be given in advance. In the two patients described, a lengthy and expensive hospital stay could have been avoided.

A CYP (cytochrome P450) working party has been set up at the azM. This working party counsels doctors in prescribing the right dose and combination of drugs. The aim is that we also provide adequate treatment for the people we prescribe drugs to. Before the drugs are prescribed, we try to predict which people have a heightened risk of developing side effects.

In future, it will be possible for someone to have a chip card with his or her DNA profile (a genetic passport: like Sherlock Holmes' fingerprint).

After the details from the genetic passport have been entered into an advanced computer program, the program will be able to indicate precisely which doses of drugs are safe for that individual, how to act in the case of combination therapy (NB, very important in view of the fact that in most cases it does not come down to one specific drug!) and which medication should be avoided.

There is already a very practical website operational offering the service. This information is not new, however it is best known among pure scientists and nonclinicians. In this case it is obvious that bringing together knowledge by close cooperation between clinicians and non-clinicians and transferring useful knowledge will lead to a more efficient and safer treatment programme for the patient.

Checklist for assessing the potential role of pharmaco-genetics in reducing the side-effects of medicines:

- regard each medicine as a potential cause of side-effects
- check whether the medicine is metabolised by a polymorphic enzyme
NB: preventing polymorphisms varies substantially from race to race
- above all bear in mind the fact that the problem can primarily emerge when two or more medicines prescribed at the same time are metabolised by the same enzyme
- consider checking the blood concentration of medicines from which side-effects can be expected

Near future:

- more specific prevention of side-effects of medicines
- genotyping prior to the prescription of medicines
- meticulous individual dosage advice based on the route results of the genotyping and medicine metabolism, especially in the case of combination therapy

This may sound like being a long way away, but it is closer than we think. Within a number of years, genotyping will be used to put together a unique genetic passport and it will be used in made-to-measure drug prescriptions in everyday practice.

Social relevance

The integration of these technical possibilities in caring for chronically sick patients can prevent a great deal of suffering and reduce costs. Recently, a report was published arguing that about 30% of hospital admissions are related to the wrong use of drugs. Some of these cases involve patients with lung disorders. For these breathtaking contacts, it is especially important: prevention is better than cure. Here too there is an important role for prevention management.

Future research

To recognise a problem, it is first of all important to formulate a good definition of the problem. In order to reach a good definition, effective measuring techniques are needed. Future research will comprise searching for new measuring methods in order to record the problems of patients better. The overreaction of the natural immune system should be regulated and lowered. It is important to find the causes of this overreaction and – if possible – eliminate them.

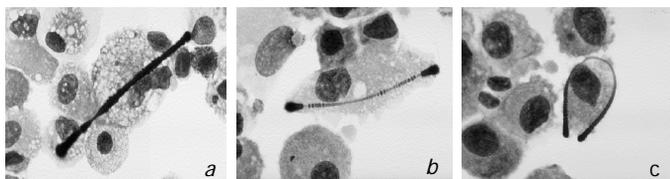


Figure 14 – *Battle between an asbestos fibre and an alveolar macrophage (AM or eater cell present in the lung). The cells and fibres shown were found in bronchoalveolar lavage (BAL) fluid acquired when rinsing a lung. a) asbestos fibre near an AM, b) the AM tries to destroy the asbestos fibre, c) now who won: the AM or the fibre?*

This is however not always enough. Sometimes it concerns substances that the body cannot break down, such as aluminium and the previously mentioned insulation materials asbestos, rock wool and glass fibre (figure 14). These substances remain in the body after inhaling them and form a continuous irritation. These fibres can cause all kinds of harmful reactions, release substances harmful to the body and lead to oxidative stress. In this case, there

is a need for food and drugs that are able to suppress the harmful reactions in the body. This means we should take a different look at the illness and its course and future research should also be focused on finding adequate and usable anti-oxidants.

Treatment opportunities and top referral care

A search will have to be made for drugs that can repair the damage done to the immune system. The development of new drugs costs a lot of money. When new substances are available, it isn't always possible to prescribe them immediately. An example of this is the expensive anti-TNF-alpha therapy. Drugs with a similar effect have already earned their spurs among patients with certain forms of rheumatism and an intestinal disease, Crohn's disease. I have already indicated that it is important to make a central register of patients with complicated chronic disorders and to have treatment regulated from the centre. This should not however mean that the centre concerned, for instance the ild care centre at the azM, is held responsible for the entire costs of such a treatment unless a separate budget is made available for this.

A top referral centre should not only be able to make the best possible diagnosis, but should also provide an opportunity for advising, prescribing and applying the most suitable therapy. Last year so-called DBCs (Diagnose - Behandeling - Combinaties - Diagnosis - Treatment Combinations) replaced budget financing in the Netherlands. DBCs are care products provided by the business, in this case by the hospital. The present DBC system provides for diagnostics yet unfortunately it does not take sufficient account of expensive treatments. Expensive drugs are no longer financed separately, but should also be included in this.

New drugs are by definition expensive. The costs of investment in research have to be recovered. New drugs are launched in the majority of cases by hospitals. Therefore hospitals are the first to face the issue of high costs and confusion surrounding therapeutic and economic added value. Expensive drugs are not sufficiently covered in the reimbursement system for hospitals. In practice this sometimes means that doctors are refused permission to prescribe them. In this way doctors are unable to satisfy their care commitment in the best possible way. In addition, the result can be arbitrary. One medical insurer is willing to pay for the drug while another is not. That is socially unacceptable.

Social consequences

An important assessment also has to be made socially. If a chronically ill person is able to return to the workplace with the aid of certain drugs, even if these are expensive, then it can turn out that the treatment saves money. Especially when the person concerned no longer needs to be a burden on disability benefits.

The costs need to be weighed against the benefits. This demands close cooperation between different ministries.

Recently, I received a request from the employer of a patient to indicate what the best treatment for the employee would be. They also indicated their willingness under certain conditions to provide recompensation. The reason given was that they valued this employee so highly that they would do everything possible to get him back to work, even if it meant paying for medication that was not yet available through the insurance. Indeed, such a treatment could turn out to save money if different institutions were willing to cooperate and for instance share the costs for treatment.

Care and its provision

The complexity of the medical sciences makes it necessary to introduce increasing specialisation. Doctors are more or less forced to restrict themselves to their own special fields. A medical specialist is someone who is trained to reject a diagnosis in his/her own field. One often hears: 'it's not cardiac, it's not pulmonary' and the patient is left in confusion. This is a paradox. For as the number of possible options increases so does the complexity of patients' problems. The result is specialisation. This does not mean literally that the doctor cannot or should not stray far from home as it were. In addition, knowledge of each other's ability and cooperation is needed to interpret certain observations.

Doctors are just like artists or performers. The right dose of stubbornness, energy and willingness to seek the right cooperation every time are important characteristics. Integrity is important. In this way, interdisciplinary cooperation can improve patient care and science. Finding people who are willing to do just a little bit more despite the pressure of work can be inspiring.

At an early age I learnt *'there's no such word as can't'*. That is something I've always remembered when striving for answers, not to give up too soon. You have to dare to deviate from the norm or healthcare will become too rigid. Don't allow yourself to be pushed into a specific cubby-hole, be willing to transcend the so-called task and avoid narrow-mindedness. The pressure of time and the need to get results mean there is less chance of finding out what is really going on. This applies most certainly to complicated clinical pictures, including those of interstitial lung disease, the causes of which are not always obvious. Caring for their specific group of patients by specialists can in addition save a lot of money because they will see what the problem is and provide made-to-measure advice faster. In some cases such an approach can avoid unnecessary diagnostics.

In order to skip certain diagnostic possibilities, knowledge of the problem is necessary. This also has a down side. People should be cautious and ensure that integral and generalistic thought should continue to be integrated in specialist actions and approach to each patient whatever their question.

Improving care

A patient aged 50 reported to A&E at his local hospital with severe chest pain. The seriousness of the situation meant that the cardiologist was first asked for help. An ECG was given and some blood tests carried out. This failed to reveal any abnormality and the cardiologist reassured the patient that nothing was wrong with the heart. In view of the fact that the patient indicated that the pain increased with deep sighing, the lung specialist was consulted. An x-ray of the lungs and additional laboratory tests revealed nothing worrying and there was again no explanation for the complaints. The patient was given painkillers and advised to contact the GP if the complaints did not stop. In the end a specialist physiotherapist, a manual therapist, was asked for assistance. The physiotherapist found a clinically relevant block in a thoracic vertebra.

What was the need? Was it necessary? How is it possible to reach an adequate diagnosis more quickly?

Why does someone go to the doctor?
 Why is this person looking for help?
 What help is being sought?

The fact that everyone nowadays looks at the patient from a specific ‘specialist’ angle has a major disadvantage, namely that the patient is not seen. One looks at the heart, the next one looks at the lungs, but no one looks at the whole patient. This also means that someone can spend hours at A&E without any clear conclusion being drawn. The only thing that emerges after hours of evaluation and waiting is: ‘if it doesn't stop, you'd better go and see your GP.’

Medicine has seen enormous developments. Many techniques have been developed to reach a diagnosis. One of the most important characteristics of the good clinician remains the ability to distinguish between ‘okay’ and ‘not okay’, in other words when it is necessary to keep looking and when the patient can be reassured. Unfortunately we have to conclude that it is not possible to understand everything. Sometimes we have to admit we can't find it. Does that mean that ‘nothing’ is wrong or just that our present abilities do not enable us to find it? The following still applies: ‘you can't recognise what you don't know’ So if you don't know what you looking for, you can't find it. Or to quote the great Dutch soccer star Johan Crujff: *‘you only see it when you understand it’*.

Evidence-based medicine

Evidence-based medicine integrates the best external evidence and individual clinical expertise. This latter part is built up from everyday curiosity about solving problems and acquiring experience. The question is also whether all aspects of everyday (para)medical activity can be investigated scientifically. The

more or less clear areas are 'black' with evidence that something is pointless or even damaging, or 'white' with evidence that a treatment does the patient good. The area filled with dilemmas is 'grey'

Medical specialists get patients referred by the general practitioner to the outpatients clinic or to A&E. They approach a problem conscientiously, explicitly turned judge based on the evidence available. In practice this means the integration of clinical expertise and the best external evidence available from systematic investigation. They look to see whether the pattern of the complaint is familiar to them. When the pattern is not clear, doctors have to ask themselves whether the patient's health problems are part of their specialisation and whether theirs is the right discipline to tackle this specific health problem.

In view of the fact that the doctor is the primary individual responsible for deciding on the care offered to a specific patient, when it comes to all-round diagnostics, the doctor should also be aware of the competencies of other professionals in the same network. This does not just applied to doctors, but certainly also to competent paramedics, who work at an academic level thanks to additional training and/or clinical experience. This is an argument in favour of multidisciplinary networks, in therapy but also in diagnostics, with perfect cooperation between the different professionals, each making use of the others competence. The lung specialist, the cardiologist as heart specialist, the rheumatologist specialised in inflammatory complaints, the neurologist and specialist of the nervous system, the orthopaedic specialist for static and operative techniques with regard to posture and movement, the physio/manual therapist as the specialist for the function of posture and movement etc. That is why it would be a good thing if the team of caregivers involved with the front-line treatment of patients at A&E and various outpatients' clinics could be expanded to include a physiotherapist or manual therapist. The future demands even finer tuning of care offered within an organisation that is still learning.

Guidelines in practice

In medicine, a good dose of curiosity and creativity is essential. Daring to accept that acquired knowledge might not be enough and that looking further may be necessary is not always appreciated. Medicine is increasingly adopting a kind of cookery book style. Guidelines formulated ensure that actions are meticulous and well considered. That may seem noble, however the danger is that people will not think of themselves and that creativity will be lost.

Complaints linked with interstitial lung diseases are often rare and are not always recognised. This demands extensive diagnostics and a significant dose of creativity from a doctor. 'When did it start?' 'What have you been doing?' 'What have you been in contact with?' These are all questions that should be studied with meticulous care. It's not enough to ask someone's profession.

Exposure to a variety of materials, working conditions, hobbies, circumstances at home etc. now and in the past can be of great importance.

Improving and optimising facilities

In order to improve care and to ensure financing of new drugs, cooperation is essential between patient associations, professional organisations and doctors. In this case too, cooperation can lead to the provision of better-integrated care. In order to generate money in another field apart from only research grants, the old care foundation has been founded in Maastricht. The aim of the care offered by us as doctors should meet the requirements and needs of the patients. Providing second opinions and offering referrals create obligations. This service should meet the needs of the care requested. It is also important to offer referring colleagues assistance with the aim of improving the care of patients with complicated complaints.

Further improvement is possible by using the steadily growing opportunities offered by digital media. So-called e-consultations will acquire an increasingly important place in the function of a tertiary reference centre. National and international cooperation can be ideally exploited here and the costs of health care further limited.

The role of government

Lung fibrosis, in other words connective tissue or scar forming in the lungs, can lead to an extremely serious breathtaking situation. And effective treatment with drugs is unfortunately not available. Lung transplantation can in some cases be the only answer for these patients. It can turn the lucky recipient's life around to suddenly be able to function again normally, take part in sports etc. and to be actively involved with bringing up the children and able to start working again.

This brings me to a point I want to focus attention on. In the Netherlands, unlike in Belgium, people have to take the initiative themselves to become an organ donor. In Belgium, people are donors unless they have stated some objection. This means that there are more donors in Belgium than in the Netherlands. The government can contribute to improving care provisions. But we, as members of society, also need to realise what it means to offer someone a new chance and to be able to say to someone after a transplant: *'live!'*

Challenge

Inspiration, respect, motivation, dedication, commitment and passion are important characteristics. Just doing a little more makes the difference. It can take us further, just as a willingness to cooperate with different disciplines,

institutions and organisations can. And in this way we can contribute to improving health care and expanding knowledge.

Education

The department of lung diseases participates widely and in many ways in the medical and health sciences curriculum and fulfils many roles and functions. An extra dimension will be added to this. The special field of interstitial lung diseases (ild) deserves careful development and a more central place both within and beyond the field of lung diseases. Ample attention is already being given to the study of chronic disorders in general in the basic curriculum. ILD should be an integral part of this policy, reaching, in this way, 'a wider public'. To this end, students should be spurred on and actively canvassed to follow a part of their training for medical specialist at the ild care centre in azM. Various options are suitable for this. The path for this is geared to all sorts of professional organisations whose most important goal is to bring expertise in the field of ild to as many medical disciplines as possible. To this end, the following activities will be continued and developed further: 1) offering internships to, firstly, medical students at Maastricht University but also to other national and international universities and institutes, 2) participating in various specialist programmes, keeping close contact with the various professional organisations, and 3) attending to postgraduate studies both nationally and internationally.

All the ingredients that have been tackled during my oration are important for developing good caregivers, including doctors. I therefore challenge students and doctors' assistants to come and do their internship with us so that we can together try to realise this dream in the coming years.

*'...If you
can
dream it,
you
can
do it...'*

WALT DISNEY

Summary

As already indicated it is important when helping patients with interstitial lung diseases to remain creative and above all not to make do with the absence of an explanation. Keep looking, keep wondering how it can be and if necessary even make a home visit. During my training as a physiotherapist, I learned to think in an integral and holistic way, and that still gives me a great deal of pleasure. As doctors we have a wonderful profession. We are the detectives of the health care system. We have to be patient and willing – if necessary – to stray from the well-beaten path. Keep striving for the right cooperation and communicate laterally: that can lead to answers you would never have thought of.

Specialisation should not lead to blinkered thought, but should exploit the qualities of generalistic thought. Continue to strive to find explanations and solutions. Do not allow yourself to be discouraged by the pressure of work. It comes down to something unique: a patient is vulnerable, needs help and it is our task to answer that need as best we can. An appeal is also made to the patient's personal responsibility. Even when there is apparently no solution, as a caregiver you can still let patients know you're there and give them the feeling they are not alone.

Here is also an important role for providing education. Students and doctors in training should be made enthusiastic and shown that you should not make do with the lack of an answer. In order to find an explanation, you sometimes have to think of unexpected possibilities

It should be clear that I am proud of my profession and want to continue my work to the utmost of my ability, stimulated by the new opportunities offered to me today.



Figure 15 – Lung specialist to-be (MD).

A word of thanks

I want to thank my educators for their wise lessons and the valuable advice they still give me. Consultation remains crucial. In recent years I have discovered that in the azM and within the UM, an enormous number of enthusiastic people are working who are prepared to put their shoulders to the grindstone. The staff of most medical teams has proved that multidisciplinary cooperation is perfectly possible in the azM, and for that my grateful thanks. I would especially like to thank the members of the Sarcoidosis Management Team!

Contacts between pure scientists and all kinds of supporting disciplines such as the departments of radiology, pathology, clinical chemistry, haematology, electron microscopy, medical microbiology, pharmacology and toxicology have frequently led to valuable discussions and have in the end been able to contribute to solving clinical problems. Thank you all for that.

I would like to thank my doctoral students Ruth, Nicolle, Els, Snjezana and Elske for your perseverance and contribution to the research. Agnes, Judith, Kitty and Gwan, keep up the good work!

I would also like to thank Professor Miel Wouters, jack of all trades, including being head of the lung diseases department and the initiator of the Centre for chronic diseases, my colleagues, assistants, lung function assistants, the staff of the Department of clinical neurophysiology, nursing, outpatient assistants, secretaries, Tiny and the study nurses Ester en Gé. The audiovisual services and computer service staff was at times indispensable.

An important development I would like to pause and mention is the support for the research line into interstitial lung diseases by the board of the azM and especially the chairman Dr Guy Peeters and the faculty of the UM, especially the deacon of the faculty of medicine, Professor Harry Hillen. This ensures that the ild care centre is able to offer a service based on a broad foundation from within the azM. For that I am very grateful to all other representatives involved as well.

Dear international colleagues, dear mentors, dear friends, it is a great honour and pleasure that you are present today and did not hesitate to travel to Maastricht. I appreciate this very much. Without your support and challenging discussions I would not stand here today.

The patients who have for years entrusted themselves to our approach and were always willing to take part in all kinds of examinations, to you my hearty thanks. Here too you can certainly say we make much more progress together!

My mother, my father and my sister are proud of me, but I am proud of you, Mama, because you guaranteed the basis of my training and were always there for us. Papa, in view of the fact that you encouraged me to fight for what I wanted and Sylvia, because despite being my little sister, you've grown to be a very strong and independent woman. Grandma, I will thank you forever, and you know why...

Marjon, you have seen my entire development and encouraged it. Even after today I will still have a great need of your support. Both our inspirations will hopefully lead to many new breathtaking contacts.

I have spoken.

Appendix

Relevant websites

Valuable website with information about all kinds of drug-induced lung diseases

www.pneumotox.com

Health&DNA. A variety of information and software to help with the safe prescription of drugs. Drug-drug and drug-gene interaction software

www.genemedrx.com

Association of Pulmonary Fibrosis Patients in the Netherlands

www.longfibrose.nl

Dutch Sarcoidosis Association

www.sarcoïdose.nl

WASOG: World Association of Sarcoidosis and Other Granulomatous Diseases

www.pinali.unipd.it/sarcoid/

Department of respiratory diseases azM, Maastricht

www.pul.unimaas.nl

The azM ild care centre and the ild care foundation

www.ildcare.eu

The **ild care foundation** (interstitial lung diseases including sarcoidosis and lung diseases related to occupation and environment management and research foundation).

The aim of this foundation is to optimize the care of patients with interstitial lung diseases, to broaden knowledge and to support research on the impact of interstitial lung diseases on patients and their relatives. Research on possible causes and heredity will be stimulated. Development of new therapeutic possibilities will be initiated.

Contributions to support the **ild care foundation** will be gratefully accepted and can be donated to:

Bank account number: ING (International Netherlands Group) **65.34.34.642**

To the credit of **ild care foundation** Maastricht
Mentioning your name, address and e-mail address

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