Report 2017

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Verein für Krebsforschung
Forschungsinstitut Hiscia

Society for Cancer Research
The primary aims of the Society for Cancer Research are assuring, optimizing and developing holistic cancer therapy on the foundations of anthroposophic medicine and pharmacy.

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Report 2017

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Editorial

Dear readers!

2017 marks the centenary of cancer treatment with mistletoe extracts. What has been achieved in the past hundred years? This year's annual report of the Society for Cancer Research offers a cross-section of achievements so far, and at the same time an outlook on developments we hope to undertake in the forthcoming years.

In 1917 Ita Wegman began to use mistletoe to treat patients in her Zurich practice. From there, mistletoe therapy first established itself in Arlesheim and then spread further through Switzerland, into Germany, the rest of Europe, and many other countries of the world. Three articles in this report illustrate the use of mistletoe therapy in various places in Switzerland: the site of its historical beginnings in Arlesheim, Scuol district hospital, and Berne University's hospital Inselspital.

The positive empirical experiences of physicians and patients with mistletoe therapy, as gathered and compiled over the last 100 years, must today be documented and proven by means of scientific trials and research. Various articles here reflect current achievements in this field, both in relation to humans and also animals affected by cancer. In brief summary, all studies show that mistletoe therapy leads to a marked improvement in quality of life and a clear increase in survival periods. It sometimes seems surprising that a cancer treatment can achieve both these at once, since conventional therapies are usually associated with a marked reduction in quality of life. We need further research projects to explain the underlying principle behind these positive effects, which is not yet fully apparent to the scientific world. In this year's annual report you will also find articles that relate to this theme.

Knowledge of the positive effects of mistletoe therapy, as proven in current medical studies, is not yet widespread amongst either physicians or patients. In our view, therefore, we need to improve and develop the way we communicate both the potential – and also the limits – of both anthroposophic cancer remedies and complementary treatments in general. We see it as a task of the Society for Cancer Research to meet this need by offering objective information. In the next few years we hope that a completely new website, among other things, will play its full part in such communication. For this anniversary year of mistletoe therapy, the logo of the Society for Cancer Research was also redesigned.

The chief aim of the Society for Cancer Research is to assure, optimize and develop a holistic cancer therapy based on anthroposophic medicine and pharmacy, with the use of pure, natural raw materials. In the following pages, in various articles, you will find short reports on ongoing projects. Besides examining ways to assure mistletoe stocks, and manufacturing optimization, these also include the development of new medicines. In addition, work is being done to develop new scientific approaches and methods needed for holistic research.

Globally there are only a few organizations that seek to develop new medicines and therapies for the holistic treatment of cancer, and succeed in doing so to the point where these are granted legal registration. Since natural medicines usually cannot be patented, the pharmaceutical industry shows little interest in research and development in this field, given that there is no guarantee that sales income will cover the necessary investment costs. The Society for Cancer Research regards its activities as serving the public interest. We use your donations and contributions conscientiously to achieve our aim of developing holistic, effective and well-tolerated forms of natural cancer treatment. Donations to the Society for Cancer Research are tax-deductible in Switzerland. In Germany, thanks to our sister organization, the Society for Clinical Research in Berlin, this possibility now exists there too.

We thank you for your interest and your kind support.

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The future potential of anthroposophic medicine: developing new preparations for treating cancer patients

DR. KONRAD URECH, DR. JAKOB MAIER

Rudolf Steiner, the founder of anthroposophy, was keenly preoccupied with mistletoe for many years, and from an early stage recognized its potential for curing cancer [(1)]. From 1920, anthroposophic medical activities initiated especially by physician Ita Wegman gave him the opportunity to present his spiritual-scientific research on cancer and its treatment, and to realize this in practice. The conceptual foundations that developed in the process open up a fundamental new approach to an understanding of cancer and its treatment. This wealth of accounts by Rudolf Steiner includes proposals for developing various oncology preparations, among which are some that have not yet been realized. For this reason, a new main focus of research and development has been established at the Hiscia Institute of the Society for Cancer Research: «Development of new preparations for treating cancer patients».

In order to offer an overview of this broad field and its great potential for new developments, we present below some possible new projects based on Rudolf Steiner's research. These developments of new preparations and their corresponding clinical applications relate primarily, to begin with, to mistletoe.

The chief focus of our research and development work is on realization of a suggestion which Rudolf Steiner made when he established the foundations for mistletoe therapy in the first medical course. He suggested that the glue-like substance of mistletoe (called viscin) should «in par-

Fig. 1: Blossoming Creeping Jenny (Lysimachia nummularia) in May
Foto: K. Urech

ticular» be processed into a mistletoe preparation [2]. The special pharmaceutical challenge of the relevant project here lies in the liposoluble character of viscin. To use a preparation containing viscin – which in itself is absolutely insoluble in water – must be incorporated either in a fat-dissolving base or in an aqueous emulsion. We are pursuing both these possibilities. A detailed report can be found in this issue on the «The glue-like substance of mistletoe – research emphasis of the Hiscia Research Institute». Rudolf Steiner expected that incorporating the various forces of mistletoe, including its glue-like substance, into an injection, would produce a preparation which is generally effective for carcinomas. It became apparent to us after developing a viscin ointment, that also external application of viscin can lead to cure a tumour. This was observed in the treatment of white skin cancer (basal cell cancer) and cutaneous squamous cell carcinoma with the viscin ointment developed in the context of the new research focus [3]. Thus we succeeded in proving, for the first time, that the glue-like substance of mistletoe recommended by Rudolf Steiner has an anti-tumor action.

Mistletoe preparations such as Iscador are usually given as injections under the skin (subcutaneous). But the evolution of cancer highlighted by anthroposophic insights point to the usefulness of other modes of application too. Thus in the specific situation of a brain tumour, Rudolf Steiner himself referred to the possibility of administering mistletoe extracts orally. Then also there is the possibility in oncology, rarely considered, of introducing mistletoe preparations directly into the neurosensory domain of the skin through intradermal injections (injections into the skin itself, so-called «whealing»). In the context of anthroposophic understanding of the reciprocal action of the neurosensory and metabolic realms, this is a promising procedure specifically in the treatment of tumours. For therapy of degenerative joint diseases such as arthrosis, intradermal injection of mistletoe extracts has proven to be highly effective, and far more successful than other treatments. And finally let us mention introduction of mistletoe preparations into body cavities (intracavitary), e.g. for superficial carcinoma of the bladder mucosa, carcinosis in the pleural cavity of the lungs, or in the abdominal cavity. All these particular applications require mistletoe preparations especially optimized for this purpose; and this presents a broad field for development relating to factors such as host tree, manufacturing process or application method.

The way a host tree influences the pharmacological and clinical effects of mistletoe is a subject on which much work has already been expended. Despite this, there remains a great need for further research and development, and this includes the study of new host trees for treating specific cancer types. Recently, for example, an Iscador preparation from the black locust tree or false acacia (Robinia pseudoacacia) has become available as an extemporaneous remedy. This tree is one of the most important mistletoe host-tree species in France. As a member of the pea family, it is striking for its wealth of blossoms. It has a special affinity with nitrogen and the ability to take root on very nutrient-poor soils as a kind of pioneer plant. A reference from the early phase of mistletoe therapy led our focus to develop a mistletoe preparation from this host-tree which is applied in cancer of the oesophagus.

These hints to potential new remedies made from mistletoe, and the more specific forms of application involved, can show that great exertions are still needed to unlock the full healing potential of mistletoe and take it further than has so far been achieved. Work on optimizing pharmaceutical processes for processing mistletoe into Iscador pursues the same goal. This is another research focus at the Hiscia Institute, and one that is described elsewhere in this issue.

Rudolf Steiner expressly stated that other medicines besides mistletoe can be drawn from all three kingdoms of nature (plants, animals and minerals) to treat cancer patients. His suggestion of the Christmas Rose (Helleborus niger) for treating carcinomas in men has already been realized. But so far his remark that Helleborus foetidus (Bear's Foot or Stinking Hellebore) would be even more efficacious has largely been ignored.

A note paper of Rudolf Steiner documents the specific ingredients of an ointment formula for treating open cancerous ulcers, based on larch resin, Creeping Jenny (Fig.1), thyme and beeswax. There are also a whole series of medicinal adjuvant therapies which Ita Wegman undertook on cancer patients, in collaboration with Rudolf Steiner, at the Clinical-Therapeutic Institute in Arlesheim. These include an injectable lichen remedy made from

Cetraria islandica (Iceland moss). Two further therapies show the importance, referred to above, of the skin as a neurosensory organ in cancer: a large number of cancer patients at the above mentioned Institute were given sulphur baths; and to treat diabetes and metabolic syndrome (which can both be regarded as pre-cancerous conditions) Rudolf Steiner recommended rosemary baths. He also made suggestions for cancer remedies drawn from the animal kingdom, though this is beyond the scope of the present article.

This brief survey of just some of the possibilities for developing new complementary treatment of cancer patients shows clearly that there is still a great need for further research if we are to realize the promising potential of these approaches.

The broad range of themes currently seems to necessitate us restricting our work to a few key projects. Each of these projects requires interdisciplinary collaboration in the fields of pharmaceutical development, pharmacological research and clinical fundamentals, and the collaboration between physicians and pharmacists will be of key importance here. Staffing and financial resources will also certainly play a decisive role in determining project emphases. The new possibilities arising through the re-organized framework of the Hiscia Research Institute within the Society for Cancer Research, and the first clinical successes of our developmental project with a viscin ointment, mean that we can look forward with confidence to the future development of this work. ■

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What anthroposophically extended medicine can achieve in a university hospital

PROF. DR. URSULA WOLF

Therapeutic mistletoe injections were first trialled 100 years ago. It was Dr. Ita Wegman, the untiring creator and pioneer of anthroposophically extended medicine, who took up ideas from Dr. Rudolf Steiner for a drug for cancer patients. As early as 1904 Rudolf Steiner had repeatedly spoken about the special characteristics and potential of mistletoe in comparison to other plants. Together with the pharmacist Adolf Hauser, Ita Wegman developed the first injectable mistletoe preparation, known as Iscar, which she administered to patients with various cancers at her Zurich practice in 1916/1917. She documented this use in case descriptions.

Mistletoe injections were increasingly used for patients with cancers at the Clinical-Therapeutic Institute (the future Ita Wegman Clinic) in Arlesheim and, over time, at other institutions in Switzerland and abroad. Development work continued on the original injectable mistletoe preparation as the pharmacological processes were refined and a complex machine built especially for the purpose. The preparation finally became available in the form we know today as Iscador.

Over the decades, mistletoe therapy continued, evolved and is still in use today, 100 years later. The effect of Ita Wegman's impetus for an injectable mistletoe treatment is ongoing, with mistletoe therapy now established in Europe and elsewhere, including on other continents. Various institutions have to this day a tradition of vigorous research on mistletoe as a plant and on mistletoe preparations beyond clinical applications. As a result mistletoe preparations have become the best researched and most frequently used complementary medicine in the German-speaking and central European regions.

Mistletoe therapy is typically used in practices and hospitals with an anthroposophical medical orientation, but also in primarily conventional medical institutions. One prominent example is its use in patient care by the professorship for Anthroposophically extended Medicine at the University of Bern.

Professorship for Anthroposophically extended Medicine at the University of Bern

This professorship which is specifically dedicated to Anthroposophically extended Medicine was created in 2014. Professor Ursula Wolf from the University of Bern was selected as its first incumbent by the ordinary appointment process. Ursula Wolf has also been Head of the Department of Anthroposophically extended Medicine since the departure of the greatly skilled Professor Peter Heusser in 2009, who led the department within what was then the «Collegiate for Complementary Medicine».

The professorship for Anthroposophically extended Medicine is today part of the Institute of Complementary Medicine (IKOM). The former Collegiate for Complementary Medicine was converted into the Institute of Complementary Medicine in 2013 on the merits of its strong academic performance. The main tasks of the professorship for Anthroposophically extended Medicine relate to research and teaching. Professor Ursula Wolf and her team of outstanding scientists plan, carry out and publish research on a range of topics.

Studies include questions of basic research (e.g. on the physical characteristics of medicines and original substances), patient-centred research (e.g. the effect of speech therapy on human physiology), and clinical research (e.g. the effect of speech therapy on patients with asthma, or the effect on patients of medicines such as Weleda's Euphrasia-Augentropfen® in clinical practice).

In the domain of teaching, introductory and foundation lectures on anthroposophically extended medicine form part of the mandatory curriculum for medical students, who can also choose to take supplementary elective courses. In addition, the professorship offers and supervises master theses and dissertations on topics from complementary and anthroposophically extended medicine.

Professorship for Anthroposophically extended Medicine in practice

Under the professorship of Anthroposophically extended Medicine, Professor Ursula Wolf and her fellow physicians advise and treat patients on the premises of the Inselspital, Bern University Hospital, either as outpatients or on the wards of the Inselspital, using available anthroposophical medical therapies – including mistletoe therapy in the case of cancer.

Fig. 1: Building at the Inselspital hospital where patients receive anthroposophically extended medical consultations.
Photo: Estelle Langer, AEM-IKOM

Fig. 2: Prof. U. Wolf in consultation with a patient.
Photo: Estelle Langer, AEM-IKOM

Outpatients are mostly referred to the anthroposophical medical consultations by the Bern University Hospital (Inselspital) but also come from other hospitals and private practices. This enables many patients to benefit from mistletoe therapy and other treatments using anthroposophically extended medicine.

These days, Professor Wolf and her team enjoy a good level of exchange and collaboration with the conventional medical oncology departments and practices. It took many years to lay the foundations and achieve this state, however. Contacts had to be made with the oncology teams, the meaning and content of anthroposophically extended medicine, and particularly mistletoe therapy, had to be explained and made comprehensible, trust had to be built, preconceptions broken down and concerns and reservations clarified. Ultimately we had to prove ourselves through our actions to the patients, their families and relatives, as well as our medical colleagues, therapists, nurses and others.

Rising demand has meant that outpatient consultations are now held at Inselspital on every working day of the week. It is still true to say that demand for mistletoe therapy mostly comes from the patients themselves rather than directly from the oncologists treating them. The level of knowledge about mistletoe therapy is in general still limited in conventional oncology and the attitude of physicians tends to range from caution and reserve to occasional, but increasingly rare, dismissal.

However, conventional oncologists are increasingly recognising the effects of mistletoe therapy in terms of improving patients' quality of life and general state of health, as well as softening the side effects of chemotherapy and radiotherapy. One reason for the reticence in conventional medical oncology is that mistletoe preparations are what we call multi-component substances. These can trigger a variety of changes in the immune system, for instance in white blood cells and natural killer cells, as well as at the level of messengers such as interleukins. Conventional oncologists may be unclear on when and under what circumstances effects occur. This can cause uncertainty and a lack of trust in mistletoe therapy, which in turn leads to a cautious attitude.

With regard to the action of mistletoe preparations at a physiological, immunological and metabolic level in the human being, it would be a good thing if knowledge about the effects of mistletoe therapy and various mistletoe preparations were to be extended. Hence it is important that research activity in the field of mistletoe therapy should be continued and expanded in these fields.

Further development of mistletoe therapy and anthroposophically extended medicine

The potential of mistletoe therapy and anthroposophically extended medicine in cancer has not yet been exhausted. It would certainly be worth conducting new and more profound research into other medicines and preparations as they are used in anthroposophic medicine. It is conceivable that new substances might be discovered and developed into medicines to treat people suffering from cancer. Federal funders such as the Swiss National Fund, the Swiss Cancer League and the Commission for Technology and Innovation are a welcome and necessary source of support for research projects in this field.

Research activity to develop mistletoe therapy, mistletoe preparations and other potentially new medicines suitable for cancer treatment is just as much a task of anthroposophically extended medicine as its clinical work. This really demonstrates that anthroposophically extended medicine is a school of medicine that continues to evolve.

I wish all those working on the further development of mistletoe therapy continued determination, excellent ideas and success so that mistletoe therapy can fulfil its original promise and potential for our patients. ■

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Can I perceive mistletoe so that it finds itself again in pharmaceutical procedures?

Insights from fundamental research in anthroposophic botany

DR. HARTMUT RAMM

Fundamental research in anthroposophic botany at the Hiscia Institute involves enquiry into the importance of mistletoe for the human being, based on Goethean and scientific methods but also on traditional knowledge and practices drawn from mythology and the history of medicine [1]. Our point of departure is Rudolf Steiner and his spiritual-scientific suggestions relating to mistletoe and cancer, and our goal is to continually render fundamental anthroposophic botanical knowledge productive both for mistletoe pharmaceutics and mistletoe therapy.

Optimum soil for oak mistletoe cultivation

At the botanical department of the Hiscia Institute, our prime focus since 1976 has been the cultivation of oak mistletoe. This pioneer project threw up fundamental questions and challenges about the plant's growth and development. As cultivated oaks on calciferous Jurassic soils near Arlesheim died off, and mistletoe seedlings grew only sparsely on the surviving trees, we slowly began to investigate soil conditions at as many natural oak mistletoe sites in France as possible. Since then, data from well over 100 sites demonstrate that the great majority of French mistletoe oaks grow on acid soils distinguished by high levels of plant-available iron and manganese. Jurassic soils, by contrast, contain a high degree of calcium, which can trigger a manganese and iron deficiency in oaks especially. In expanding our cultivation areas, therefore, we now favour sites with acid soils [2].

After 40 years of cultivating oak mistletoe, we have a markedly higher percentage of mistletoe-receptive oaks at cultivated sites with acid soil than at sites with alkaline soils. While the oaks' ge-

On branches of resistant oaks the mistletoe germ «starves» (left), whereas it can embed its haustorium in the branches of mistletoe-receptive oaks (right).
Photos: H. Ramm

Spraying biodynamic horn silica preparation on the crowns of mistletoe-bearing oaks and elms.
Photo: H. Ramm

netic disposition may well be responsible for their lack of physical and biochemical resistance factors in the bark, the vitality of these oaks is clearly of importance for the growth and further development of mistletoe seeds, and this in turn is dependent on soil conditions.

Mistletoe growth and medicinal quality

Drawing on detailed investigations of developmental processes in the mistletoe haustorium – the organ comparable to a root – we tried to better understand the role played by the supply of specific mineral nutrients in establishing the mistletoe on oak branches [3]. Here we came to focus on the tree's cell division zone, called the cambium, which is responsible for the mistletoe embedding itself in the young wood. References in the literature emphasize that a good supply of manganese, in particular, is important for cell division activity. The manganese deficiency triggered by too much calcium on alkaline soils at some of our cultivation sites therefore led not only to small, yellow mistletoe leaves but also to a reduced cambium activity in the oaks, leading to inadequate growth of the trees and likewise to weakened mistletoe growth.

Whereas leaf analyses showed that other deciduous trees such as apple and elm are not dependent on manganese to the same degree as oaks, it seemed advisable to us to enhance manganese metabolism in oak mistletoe cultivation sites in a targeted way. These measures range from activating the microflora in the roots of the oaks by adding compost, through harmonizing life processes by application of biodynamic preparations up to embedding important cultivation stages into oak-specific cosmic rhythms. Combining all relevant activities will, we hope, improve the development of mistletoe bushes, thus making harvesting easier and, not least, improve the quality of mistletoe and the medicine made from it.

Mistletoe developmental processes and harvesting times

In four decades of practical oak mistletoe cultivation, we have learned that the mistletoe bushes develop extremely slowly. Only 10 years after sowing mistletoe seed, at the earliest, can one harvest any appreciable quantity of berries. In general this is due to the strongly compressed shoot growth of the white-berried mistletoe. Detailed investigations of the formative process in the mistletoe shoot have shown that this strongly compressed form of the mistletoe branch is determined in the leaf axes already during the early development of the primordium. Decisive here is an early-stage reconfiguration from vegetative leaf formation to generative inflorescence. The associated tendency to internalization always manifests in the weeks prior to the summer solstice. But in June, also, formation of viscotoxins in the new, unfolding mistletoe leaves, reaches its maximum level [3]. Correspondingly, harvesting of the summer mistletoe crop for Iscador manufacture takes place in the same month. Morphological and pharmacological tests help to more precisely specify the harvesting period for summer mistletoe proposed by Steiner.

The typical mistletoe branch is strongly compressed and consists only of a stalk with two bilateral leaves and an inflorescence from which the fruits ripen in autumn.
Photo: H. Ramm

Polarity – from form through substance to pharmaceutical processing of mistletoe

Morphological and pharmacological tests have revealed polar gestures also in the spatial form of the mistletoe bush: viscotoxins arise in the young leaves and compressed flower bracts at the periphery of the bush, which take the place of the numerous leaves common in blossoming plants. By contrast, mistletoe lectins gain greater concentrations as the stalks of the mistletoe bush grow older: they achieve their relative maximum at the centre of the bush where, instead of an ordinary root, the haustorium characteristic of the mistletoe forms a connection with the host tree. Both mistletoe toxins also reveal opposite gestural actions in cell cultures: viscotoxins dissolve the outer membrane of cells while mistletoe lectins halt protein metabolism inside cells. From this we derived the working hypothesis that the formative forces at work in the viscotoxins normally express themselves in leaf development and are centrifugally oriented. We see mistletoe lectins, on the

other hand, as the bearers of metamorphosed formative forces which ordinarily act in root and wood formation, and are centripetally oriented [3].

Mainstream botany describes the underlying polarity as (positive) geotropic root growth and negative geotropic shoot growth. In relation to plant metamorphosis, Goethe speaks of contraction and expansion. In his cosmological botany [4] Steiner sees sun and moon as the cosmic sources of these archetypal polarities of forces, which have, for example, been practically applied for millennia in Chinese medicine as yin and yang. Anthroposophic mistletoe pharmaceutics extend the natural polarity of forces at work both in the development of mistletoe's form and substances, and in the seasons of the year, by means of a technically demanding, polar pharmaceutical process: the extract of summer mistletoe falls in single drops vertically downwards from above while, in polarity to it, the winter mistletoe extract spreads horizontally outwards at great speed as a thin film of juice. The falling summer mistletoe drop enhances the tendency to internalization active in the mistletoe plant in June, while, in polarity to it, the outspreading film of juice strives breadthwise outwards and overcomes the winter mistletoe's tendency to be entirely centred within itself. In accordance with the principle of polarity and intensification, new qualities arise as these opposite tendencies interpenetrate intensively [4]. These new qualities enhance the natural properties of mistletoe. Tests undertaken with pre-damaged plant seedlings showed that the Iscador machine process can indeed trigger a greater protective action than summer and winter mistletoe extracts simply mixed by hand [5]. It will be an important task for the future to chart this new kind of quality more consciously in the therapeutic process.

From outward knowledge to inner stance

In passing from precise observation to interpretation of the metamorphic process in mistletoe pharmacy, anthroposophic botanical research departs from the safe world of tangible phenomena, and instead approaches the boundary of a still emerging world. In inner engagement with plant development processes, we can inwardly grasp this threshold at the transition between vegetative unfolding and generative internalization. In order to assess what the new type of emergent qualities are here and what conditions can help them manifest, we must also adopt a new cognitive orientation. Starting from the seasonal cycle, whose summer and winter polarity is reflected in the development of mistletoe's substances and form, a small, regular study group practises together to experience transformation processes in nature as inwardly

In winter, the white-berried mistletoe is most strongly emancipated from its host tree.
Photo: H. Ramm

Seek thou the highest, the greatest?
What the plant is involuntarily
Be wilfully.
That's it!

as possible, on the one hand, and on the other to feel our way towards related processes of transformation in the human psyche. This work and study is based on the 52 weekly verses of Rudolf Steiner's Calendar of the Soul, which starts every year with the Easter impulses of renewal. In the first 26 weeks, these verses invite the soul to release itself, firstly, from habitual knowledge and intentions, and to give itself up, as if imitatively, to a nature experienced as a mothering being.

After Michaelmas, however, the soul is prompted to emancipate itself from the outward course of nature's cycle. Its goal now is to refine and enhance through inner activity the forces taken up through our inner devotion to nature. An important step on this path involves developing a new kind of questioning stance towards nature. The question uttered in the verse for the first week of December can be transferred as below to the nature of mistletoe and mistletoe pharmaceutics.

Can I perceive existence
So that it finds itself again
In soul's creative urge?

Can I perceive mistletoe
So that it finds itself again
In pharmaceutical intentions?

In these exercises, fundamental anthroposophic botanical research, complementing the practical work of oak mistletoe cultivation, is enlarged to include cultivation of inner capacities which can be described as conscious introversion, humility and transparency. In his own day, in spiritual dialogue with Goethe, Friedrich Schiller formulated the underlying motif as follows:

Seek thou the highest, the greatest?
What the plant is involuntarily
Be wilfully.
That's it!

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Young mistletoe bush on spring whitethorn. Photo: H. Ramm

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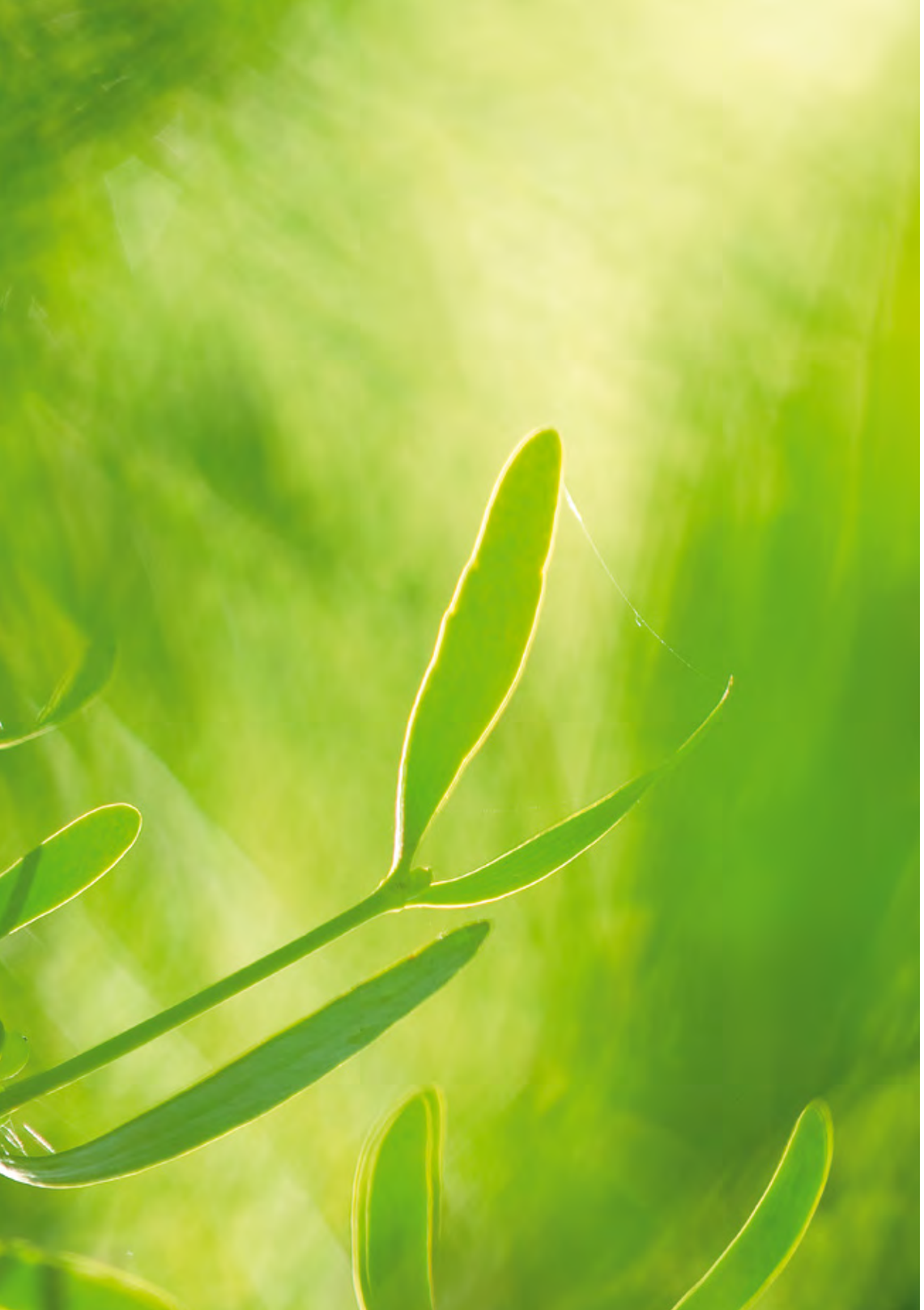

Historical results from cancer treatment with mistletoe extracts

Clinical reports on mistletoe therapy since 1924

DR. WILFRIED TRÖGER, DR. MARCUS REIF

In 1917, physician Ita Wegman first gave breast cancer patients a mistletoe extract that developed into the preparation Iscador M in use today. In doing so, she was following a recommendation from Rudolf Steiner, who suggested that the mistletoe should be harvested in summer and winter, and combined in a specific manufacturing process to make an injection preparation. He opined that this remedy would have the potential to «replace the surgeon's knife».

In view of this ambitious therapeutic aim, in the early days there were many reports of the effects of mistletoe therapy on tumours, and partial or complete remission of the tumour process was frequently reported. No doubt observations were also made of the general state of patients, but they were scarcely mentioned in these early reports on the results of mistletoe therapy. One exception here is a clinical report on the use of «Cancerodoron» published in 1924:

It became apparent that, without exception, injections of the new medicine have a beneficial effect on the patients' general condition. Attacks of weakness previously experienced as severe conditions give way to a subjective sense of wellbeing, and severe pain ceases. In many cases patients receiving the new injections were pleased to relinquish the morphium injections which they had previously regarded as indispensible. Their appetite improved and they gained the feeling that their condition was improving. From all our observations it is apparent that a major subjective improvement is obtained. [1]

While this report of the therapeutic efficacy of Iscador for cancer patients may be familiar to us, it first had to be acknowledged and confirmed as a distinct therapeutic aim over many decades of

clinical practice with Iscador. Is it possible that doctors in those days regarded this finding as a self-evident concomitant of the tumour treatment, and therefore did not regard it as worthy of any further mention?

The four diagrams reproduced here (diagrams 1-4) show the quality of life parameters of two patient groups – one of which was treated with optimal symptom reliefing therapy and the other also with Iscador. Here a modern scientific methodology demonstrates the effects of mistletoe therapy which have been described since 1924. The quality of life of these patients with advanced or metastized pancreatic carcinoma were recorded using the Core Questionnaire of the European Organization for Research and Treatment of Cancer [2].

But the self-evident fact that an improved general condition is associated with successful tumour treatment was turned completely upside down from 1949 onwards with the emergence of antitumoral chemotherapy and its multiple undesired side effects. During chemotherapy, severe accompanying symptoms are regarded as the un-avoidable expression of the antitumoral action. The intensity of this treatment is increased to an only just bearable level, in the hope of maximizing the efficacy of chemotherapy.

The sometimes dramatic side effects of such antitumoral therapies were not without consequences for clinical research. From 1980 efforts developed to document and treat symptoms associated both with the disease and its treatment. For this purpose questionnaires were developed which can record the daily quality of life of patients affected by these symptoms. Questions relate here to their mobility, social, emotional and cognitive capacities, and to their social capacities in family, professional and social settings. Since the 1990s, such standardized, multi-thematic questionnaires, which aim to record patients' general quality of life, became a necessary part of the standard documentation of efficacy in oncological studies.

This broadening of therapeutic goals in oncology was also taken up by mistletoe researchers. Prior to 1980 there were already single case reports on using mistletoe treatment to reduce the severe side effects of chemotherapy. Encouraged by this, studies were undertaken from 1980 that followed a fixed protocol, in which patients were randomly assigned either to the group of those treated with Iscador or those who were not [3-6].

These studies confirmed the above-mentioned findings documented in 1924, as well as in later clinical studies (diagrams 1-4).

The German legislature also recognized the relevance of these broader therapeutic goals for patients and physicians, and enshrined them in law as a decisive criterion for evaluating new medicines. Thus, under «patient-relevant changes during illness», section 35, paragraph 1, clause 1b of the 5th Social Code gives equal status to a) survival, b) disease- and therapy-associated symptoms and c) health-related quality of life. Improve-

General state of health

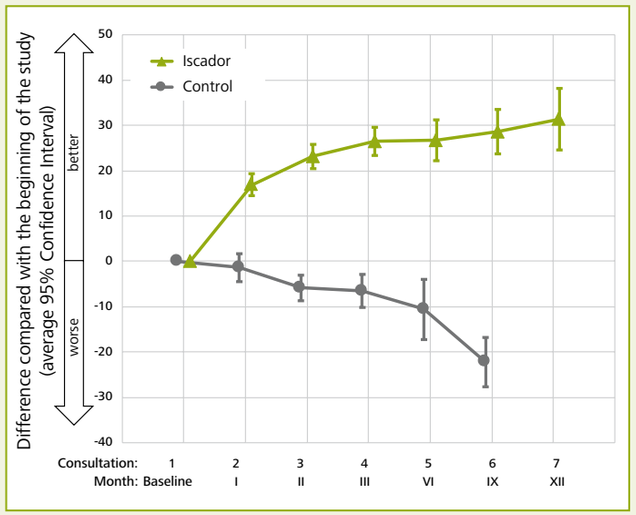

Diagram 1: General state of health of patients with pancreatic cancer with or without Iscador treatment

Fatigue

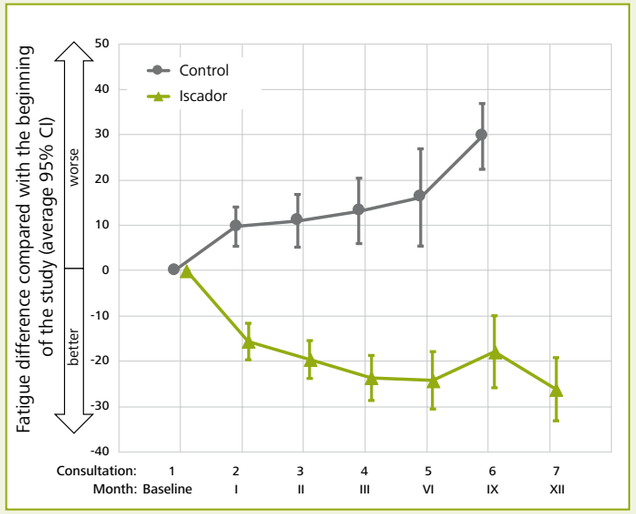

Diagram 2: Progression of fatigue in patients with pancreatic cancer with or without Iscador treatment

Pain

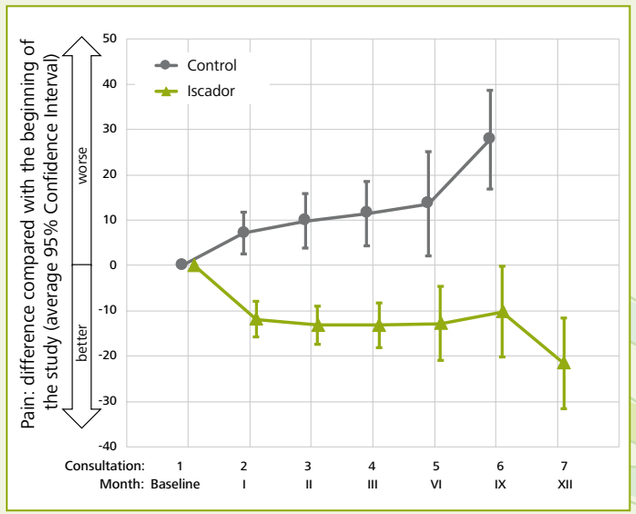

Diagram 3: Progression of pain in patients with pancreatic cancer with or without Iscador treatment

Lack of appetite

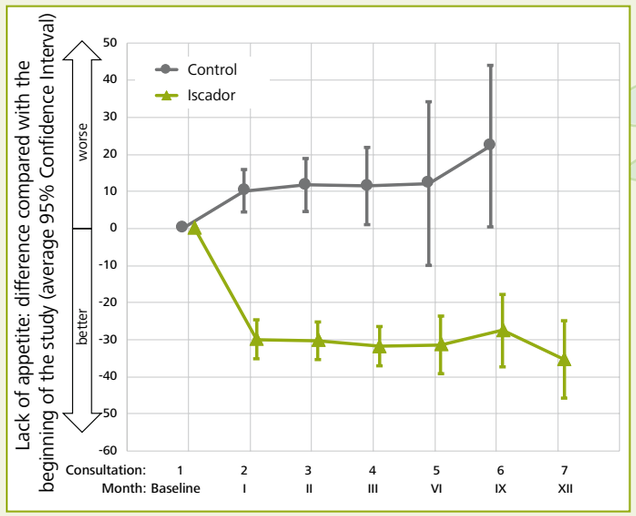

Diagram 4: Progression of lack of appetite in patients with cancer of the pancreas with or without Iscador treatment

ment in just one of these criteria is already regarded here as «patient-relevant».

With the use of conventional antitumoral therapies, it is extremely unusual – and therefore perhaps hard to understand for physicians without any experience of the actions of mistletoe therapy – for a single medication to have positive effects in all three of the above criteria. To counter the regularly expressed criticism of mistletoe therapy, therefore, it is necessary to undertake methodologically high-quality studies that encompass all these criteria at once.

The most important of these studies on Iscador preparations include ones on the significant indications of intestinal cancer, breast cancer, lung cancer and pancreatic cancer. In these studies on subcutaneous injections of Iscador, an improvement in quality of life, reduction in side effects of conventional therapies and also a marked increase in survival periods has been found [5].

Currently three studies are underway on the efficacy of Iscador for carcinoma of the pancreas and lung. Naturally these studies must adhere to the latest state of knowledge and current guideline recommendations for conventional oncology therapies. One of these studies, for instance, focuses on simultaneous treatment with Iscador and the latest conventional antibody therapies. In the near future two further breast-cancer studies are in planning to research additive Iscador treatment alongside conventional therapy. Besides the effectiveness of mistletoe therapy a direct comparison is also envisaged here between tolerance of chemotherapy with or without simultaneous Iscador treatment.

The question as to optimum allocation of limited financial means is becoming increasingly important in medicine, with clinical research intensifying its focus on the economic viability of the therapies used. Besides documentation of the clinical findings, and quality of life, therefore, studies record the resources used in treatment to compare the cost-benefit relationship of the therapies investigated. These economic aspects are ones which will also be included in forthcoming studies on Iscador.

Additionally, further research on the mistletoe preparation Iscador itself is envisaged, and on its host trees, manufacture and modes of application. To optimize the therapy, the focus of research efforts in future will increasingly be on

the diverse modes of its application: intravenous application is to be investigated alongside applications to the pleura and the abdominal cavity. Direct injections into the tumour and around it will also be the subject of clinical investigation.

Many tasks and requirements await us, arising from questions being asked about mistletoe therapy in ever broader contexts, and from the broad spectrum of actions of Iscador itself. 100 years after they were introduced, therefore, mistletoe and Iscador are set to elicit great interest and attention. ■

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Crystallization procedures in medicine

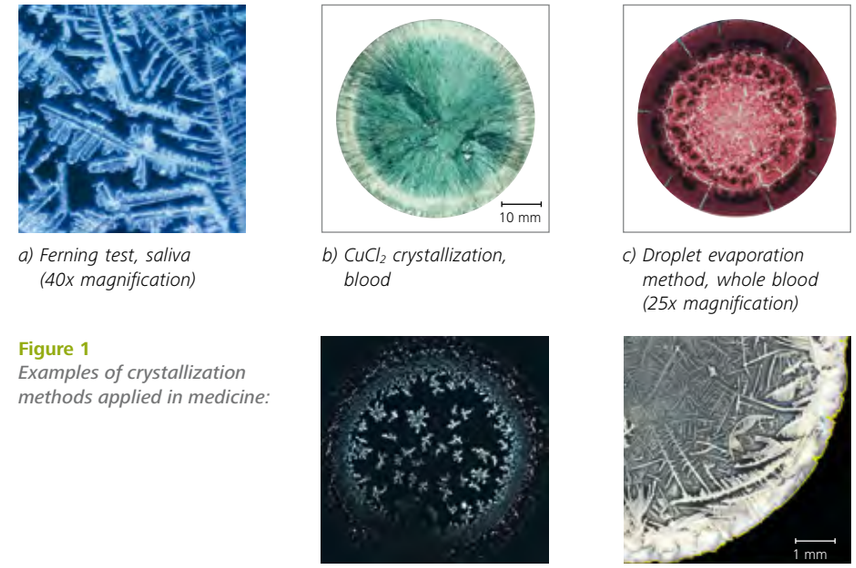
DR. MARIA OLGA KOKORNACZYK

Various processes for medical and scientific examination of bodily fluids such as blood or saliva are based on the phenomenon of crystallization. In most of these procedures, crystallization is induced by evaporation. Following this process, the crystallized residues are analyzed and evaluated. These crystallization based methods are distinguished, for example, by the volume of fluid to be crystallized, the concentration of the sample, or the presence and type of additives (e.g. copper chloride), and following these differences are suitable for diverse purposes. One can learn to interpret the crystallized residues; this may provide information about the composition of the crystallizing solution as well as the life forces present in the sample. Thus, crystallization is a holistic method.

Origin and development of the different procedures

200 years ago, already, it was known that evaporating fluids can form crystallized residues, and that these residues look different depending on the composition of the fluid in question [1]. This led to development of the «ferning tests» (named after the fact that the crystallized patterns resemble fern leaves, see figure 1a)). Ferning tests have gained recognition as useful diagnostic tests in medicine, and are still used today in various fields. The working principle underlying these tests is simple: illness causes a change in the levels of a certain substance in a bodily fluid, and as this latter crystallizes out, different forms emerge from those of a healthy subject. These forms can then be used for diagnosis. Thus, in crystallization methodology, ferning tests chiefly reflect the level of material substance (physical level). Examples of use of ferning tests are for diagnosis of mucoviscidosis (raised salt content in sweat) or Sjögren's Syndrome (changed composition of tear fluid).

The biocrystallization method (also known as copper chloride crystallization or $CuCl_2$ crystallization) suggested by Rudolf Steiner, and developed further by Ehrenfried Pfeiffer, is very different in nature [2]. Here the bodily fluid (usually blood) is highly diluted (roughly 1:1000) and combined with copper chloride. The crystal patterns produced are large (around 10 cm in diameter) and are created on round dishes. Unlike the ferning tests, a blood imaging series (analysis) can serve overall diagnosis



a) Fern test, saliva (40x magnification)

b) $CuCl_2$ crystallization, blood

c) Droplet evaporation method, whole blood (25x magnification)

d) Droplet evaporation method, highly diluted blood (100x magnification)

e) Spagiric crystallization, blood

Figure 1
Examples of crystallization methods applied in medicine:

Photos a), c) und d): MO Kokornaczyk, b) : http://www.floraapotheke-bremen.de/methoden/ (15.02.2017),
e): Franz et al. Journal of Translational Medicine 2013, 11:278;
http://www.translational-medicine.com/content/11/1/278 (15.02.2017)

of the patient, and also reflect or depict what course the illness is taking. $CuCl_2$ crystallization therefore has been, and is, greatly valued by many – chiefly anthroposophic – physicians as a supplementary diagnostic tool. Researchers in the field of $CuCl_2$ crystallization have reported that certain crystal forms can point to a sick organ (e.g. «U» forms indicate lung pathology and polygons point to heart ailments) or to a particular disease (e.g. transverse patterns indicate cancer and star-type shapes indicate inflammatory processes). It has also been observed that one can assign particular areas of a $CuCl_2$ crystallization image to specific regions of the human body, and thus localize the site of an illness or sick organ [2]. The working principle underlying these phenomena is unknown, and this is also why $CuCl_2$ crystallization has not so far been acknowledged by mainstream medicine. It is clear, however, that $CuCl_2$ crystallization, unlike the ferning tests, not only encompasses the physical level but above all gives expression to the etheric level of life forces.

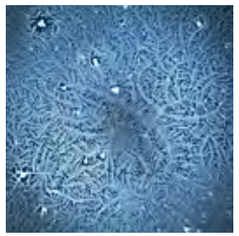
The droplet evaporation method

Apart from the two crystallization methods described above, there are other procedures which are commonly based on the evaporation of droplets. Almost all these procedures have been developed

a)

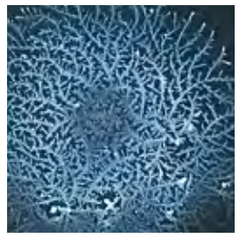
b)

c)



d)

e)



f)

Figure 2
Examples of crystallization images of a fluid containing wheat grains: a)-c) water, d)-f) potentized arsenic (D45). Images in 100x magnification

Photos: MO Kokornaczyk

in the last 20 years, partly at least because of the currently growing interest of the scientific community in the phenomenon of «self-organization» – that is, the capacity of substances to configure themselves in complex structures.

This keen scientific interest in self-organization is primarily attributable to the possibility of using it for technological purposes (e.g. fabricating nano materials and coatings) and not primarily because of its diagnostic potential in medicine. Many scientific studies on self-organization focus on the evaporation of droplets, and the configuring of substances into specific forms during this process.

There are growing numbers of studies, however, that also investigate the potential of droplet evaporation for medical purposes. Droplet evaporation methods are relatively quick, simple and diverse in use. They can be applied both to undiluted substances as well as in a range of low to high dilution. The procedure is simple: drops of the fluid to be crystallized (with or without reagents) are applied to specimen slides and dried under controlled conditions (temperature and humidity). Since many drops can crystallize at once, and their drying time is brief (around 20 minutes), many crystal images can be created simultaneously. The crystal images are subsequently examined and photographed under an optical microscope, usually in dark field. Evaluation of the images is either done visually or by means of a computer programme. The forms' complexity (e.g. the «fractal dimension») is the decisive out-come measure. Our experience with droplet evaporation shows that this procedure can encompass both the physical and etheric level.

Previous studies using the droplet evaporation method in medicine have focused on (i) medical diagnosis based on evaporation of bodily fluids (usually blood and serum) and (ii) testing of the effects of potentized medicines.

(i) Droplet evaporation applied to medical diagnosis

Studies on droplet evaporation as a diagnostic procedure (mostly applied to blood or serum; picture 1c), d)) have been undertaken chiefly for cancer (including B-cell dysfunctions, stomach and intestine cancer), but also for tuberculosis, multiple sclerosis and diabetes. The findings of these studies indicate the great potential of the droplet evaporation method in diagnostics, primarily for pre-symptomatic cancer diagnosis [3]. All diagnostical methods based on droplet evaporation are still currently at the evaluation phase, and further research in this field is urgently needed.

(ii) Droplet evaporation applied to potentized medicines

Crystal formation in droplets has proven sensitive to the effects of potentized medicines. In experiments with wheat, it was possible to demonstrate that diverse fluids into which the wheat grains were

Figure 3
Examples of droplet evaporation images
Pictures a)-c) at 100x magnification and d) at 25x magnification

Photos: MO Kokornaczyk

a) Iscador Mali

b) Iscador Pini

c) Iscador Quercus

d) Viscum album Qu-F.

placed (water, potentized water, potentized arsenic), produced different crystal forms, and that the complexity of the crystal strucutres was also correlated with the germinating capacity of the wheat seeds (figure 2) [4,5].

The droplet evaporation method at the Society for Cancer Research

At the Society for Cancer Research, we are currently undertaking studies on the droplet evaporation method. In Part I of the projet, experiments are being done on Iscador preparations, with the aim of determining suitable concentrations of the preparations in the crystallization fluid, as well as suitable crystallization conditions for the drops (humidity, temperature). Following this, we will undertake comparative experiments with Iscador preparations from different host trees, and also comparative experiments between samples from different manufacturing processes. Figure 3 shows the first crystallization images from these studies. The aim of the investigation is to produce a visible, tangible characterization of the different mistletoe preparations and their specific qualities.

In a further part of the project we want to study the potential of the droplet evaporation method for diagnosing cancer. These investigations have the long-term goal of developing a reliable early diagnosis of cancer disposition. ■

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Mistletoe therapy at Unterengadine Health Centre

Interview with Dr. med. Hannes Graf

INTERVIEW BY RAHEL WITTWER

Mistletoe therapy has been in use as cancer treatment for a century now. At the Unterengadine health centre, too, it is of key importance. How did anthroposophic oncology, and thus mistletoe therapy, arrive at Scuol as an important part of treatment?

Anthroposophic medicine had long been known in Engadine thanks to Dr. Appenzeller. He was a luminary in this field and many mainstream physicians also esteemed him greatly. Thus the ground had been prepared, and yet provision of this kind remained limited. A good 12 years ago, I was invited to develop a complementary medical department at Scuol Hospital. At that time I was working in the complementary medical ward of the regional hospital at Langnau, and originally the idea was to copy the Langnau model in Scuol. However, I wanted to take this a step further, and not «just» develop a ward or department there but offer a combination of complementary and mainstream medical provision – thus integrative medicine – throughout the hospital. Thanks to great support for this idea both from regional policy-makers and the hospital's chief physician, Dr. Gian Flury, the project was initiated in 2007 in the general medical department. And due to increas-

Personal details:

Dr. Hannes Graf is co-chief physician of integrative medicine and the therapy clinic at Unterengadine Health Centre. He is a consultant in general medicine and anthroposophically extended medicine (Swiss Medical Federation). After qualifying in Zurich, he encountered anthroposophic medicine in Arlesheim and Langnau during his consultant training. His love of the mountains led him to work at Scuol, Unterengadine.

ing demand from cancer patients, for mistletoe therapy especially, in 2015 we opened an oncology rehabilitation clinic alongside the ordinary hospital facilities. Here our focus is very much on anthroposophic therapies, and we also offer acupuncture on a smaller scale.

Chemotherapy or mistletoe therapy or both? Are there conflicts between mainstream and complementary medicine?

We are clear in pursuing the integrative medical approach. That is, we combine mainstream and complementary medicine in a way optimally designed to meet the needs of patients. Wherever mainstream medicine can offer the patient a suitable form of treatment, use is made of this, and it is accompanied where appropriate by complementary medicine. Increasingly, mainstream medicine supports this idea, since very pleasing results often ensue. Recently, for instance, we had a patient who could not tolerate the required dose of chemotherapy. But if given a mistletoe infusion beforehand, he coped with twice the chemotherapy dosage he could otherwise tolerate. This is a double benefit therefore: on the one hand he could be given chemotherapy that effectively combated his tumour, while the side effects of it could, on the other hand, be kept within due bounds.

Through experiences such as this, oncologists have become better acquainted with mistletoe therapy in clinical practice. Many have noted an increase in quality of life amongst their patients, as well as improved tolerance of their orthodox therapies.
Complementary medicine is also valuable especially when mainstream medicine has nothing more to offer. Alongside the complementary medicine department at Scuol we simultaneously opened a palliative ward, where we can care for patients through all stages of the illness right to the very end, and give them as much quality of life as possible in almost homely surroundings.

As co-chief physician for integrative medicine you have for many years been using mistletoe therapy in clinical practice alongside other cancer therapies. How do you see the role of mistletoe therapy today, and also of anthroposophic therapy?

In my experience, every cancer patient in Switzerland will sooner or later hear something about mistletoe therapy. At our hospital any patient can receive complementary therapies if they wish it. Demand remains high, and currently our case numbers are growing annually by about 10%. In the meantime Chur cantonal hospital has also started offering mistletoe consultations. Demand for adjuvant mistletoe therapy became so great that the oncologists there had to act if they were not to lose these patients to other treatment centres.

Can you tell us of actual cases where mistletoe therapy was used? What, in your opinion, are the distinguishing characteristics of this therapy?

I have found that patients who wish to have mistletoe treatment are often ones who want to actively contribute to their own recovery. In a sense, classical standard therapies are done to them, whereas mistletoe therapy is part of a jigsaw puzzle, if you like, alongside exercise, diet, artistic therapies and much more. We know from the findings of integrative medicine that it is precisely this interplay of different elements that leads to a better outcome, and can markedly increase quality of life. This may mean better quality of sleep, less pain, less nausea, better appetite, or also a better emotional mood, depending on where the problems for the patient lie or are predominant. Even when mistletoe therapy ceases after successful cancer treatment, patients often notice that they lack something, and want to begin taking it again. You can get a strong sense with these patients of an improvement in their quality of life.

What plans do you have for the future of the Unterengadine centre?

Although, or precisely because, we are in such demand, we face two big challenges: on the one hand we are victims of our own success, which is of course an excellent thing, but challenging nevertheless. The high demand means that waiting times are continually increasing, which is very regrettable both for us and the patients. So we are trying to expand rapidly; but it is not so easy to find well-trained, specialist staff, especially also because of our somewhat isolated geographical location.

The second big challenge is the rising pressure of costs. However good the idea, and however great the support, at the end of the day the finances have to be in order. This means that we will have to undertake certain rationalization measures even if this results in less than 100% accord with the anthroposophic picture of the human being. We will have to strike a balance here between standards required today and the originating idea of anthroposophic medicine.

How would you like to see anthroposophic oncology developing in future? Or, to put it another way, what needs to be done to enable cancer patients to benefit more from integrative cancer medicine?

In my view we need to drive forward clinical research above all. We need good studies that offer scientific evidence for the benefits of mistletoe therapy. This is especially important for the survival of big health centres such as the one at St. Gallen, which must also represent these methods in the public domain. We must also support the training of qualified

anthroposophic oncologists. That is, young doctors should be trained in the field as early as possible – ideally not just those interested in anthroposophic medicine, but also conventional mainstream physicians or oncologists. Patient demand has now become so high that this will surely awaken the interest of doctors too. One way in is to follow standard recommendations but be able to turn to a specialized centre for specific questions. I think that conferences with a stronger orientation toward clinical practice would be very important even for experienced mistletoe therapy practitioners. There are many luminaries in the field who possess a great store of knowledge and experience, especially in the «off-label-use» domain. If this experience could be shared more openly, we could all benefit from it.

Since marketing and sale of Iscador has moved from Weleda to the Iscador company, I have lacked various information leaflets that I used to be able to give my patients. I have an urgent need for such information material.

Finally, I would very much welcome further basic research, especially regarding the preparation's efficacy. If you recall the famous phase of Rudolf Steiner's, that mistletoe therapy should eventually replace the surgeon's knife, we still have a long way to go. Accordingly I would ask this: Are there any possibilities for developing a more effective mistletoe preparation? I believe this to be a desire of all working in the field. ■

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The fermentation of mistletoe for medicinal production

DEVIKA SHAH, PETRA ZIBULSKI

Various manufacturers offer mistletoe preparations for cancer therapy. Among them Iscador is the only one which is produced directly from freshly harvested mistletoe plants without the plants or their extracts being deep-frozen. The mistletoe is harvested twice a year in June and December (Fig. 1). Directly after the harvest, the mistletoe is exposed to a lactic acid fermentation process. This produces two extracts, a summer juice and a winter juice. The winter juice consists of a mixture of mistletoe berry and mistletoe plant extracts which are both fermented separately in November/December.

Fig. 1a: A mistletoe bush in the summer. Photo: J. Buess

Fig. 1b: A mistletoe bush in the winter with white berries. Photo: J. Buess

Iscador is the only one of all the mistletoe preparations licensed for cancer therapy which consists of extracts of fermented mistletoe. The manufacturing process goes back to a reference from Rudolf Steiner in which he describes fermented mistletoe juice from winter mistletoe as a good starting point for a very effective cancer medicine if this juice is combined with the juice of summer mistletoe. That is why the fermentation of the mistletoe plant has been an indispensable step in the manufacturing process of Iscador (Fig. 2).

Fig. 2a: Mistletoe berry mash during fermentation. Photo: D. Shah

Fig. 2b: Pressing of the fermented mistletoe berry juice. Photo: P. Zibulski

The mistletoe preparation Iscador has existed under this name since 1926. In the first decades of the production of Iscador, fermentation was left to a spontaneous, natural process of lactic acid fermentation. This procedure goes back to 1923 when the first mistletoe preparations were developed [(1)]. At that time Rudolf Steiner was shown four differently produced mistletoe extracts for appraisal (original mother tincture, trituration with lactose, fermentation with nutritional yeast, spontaneous fermentation) and he immediately favoured the mistletoe extract which had been left to spontaneous fermentation. In the light of our knowledge today, this fermentation was in all likelihood lactic acid fermentation.

It is bacteria such as Lactobacillus and Leuconostoc which set spontaneous lactic acid fermentation going as soon as the freshly harvested and chopped up mistletoe is mixed with water. In doing so, the bacteria change various sugars into lactic acid. The same happens, for example, in the making of sauerkraut or yoghurt. Lactic acid fermentation is an elegant way of making foodstuffs and plant extracts non-perishable in a natural way without heating and the addition of alcohol. There are numerous different types of fermentation in nature which are called by their end product (e.g. alcohol-, lactic acid-, acetic acid-, butyric acid-forming fermentation). Lactic acid is also formed in body tissue; it is a part of the human metabolism. It is created, for example, in the muscle cells after sporting activity.

In 1978 staff at the Hiscia Institute identified a specific lactic acid bacterium on mistletoe berries (Lactobacillus plantarum B18) which we have cultivated and propagated since then. This bacterium is added to the chopped up mistletoe in a specific optimum quantity. Through such targeted assistance the lactic acid bacteria quickly gain the upper hand over the flora of microorganisms on the mistletoe which allows fermentation to take place more quickly and consistently, and relia-

bly leads to stable extracts. Our research shows that such lactic acid fermentation leads not only to stable extracts but also to good and gentle decomposition of the mistletoe. This can be seen in, among other things, the viscotoxins, one of the two main active ingredient groups in mistletoe, being completely transferred from the plant to the extract. The group of mistletoe lectins appears somewhat reduced in its concentration but in stable and in clinically relevant doses [2].

Although Iscador has been proven to be a good and effective medicine (see e.g. [3]), the research department at the Society for Cancer Research continues to seek to optimize the action of Iscador. Since the fermentation of the mistletoe is a crucial step in the production process of Iscador, much attention is devoted to this process. The plant fermentation product is influenced and changed by numerous parameters, such as for example temperature or atmospheric composition. The research department is investigating various question connected with fermentation, such as the influence of accompanying bacterial flora of mistletoe plants on the fermenting mistletoe extract. The findings obtained about lactic acid-producing fermentation in medicinal plants (mistletoe in this instance) give us important information which we can equally apply to other medicinal plant fermentation, such as Helleborus or Cetraria. ■

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A century of mistletoe therapy – 18 years of veterinary mistletoe research at the Research Institute for Organic Agriculture

The veterinary mistletoe research group at the Research Institute for Organic Agriculture (FiBL) has been in existence since 1999. It started by investigating the use of Iscador as immune treatment for chronic udder inflammation in dairy cattle. In the course of this study it became apparent that cows tolerate this remedy well, without side effects. Since 2001, the action and tolerance of mistletoe treatment has been subject to wide-ranging study especially in cats, dogs and horses.

DR. OPHÉLIE CHRISTEN, ULRIKE BIEGEL

Mistletoe therapy for dogs and horses

In relation to domestic pets, feline fibrosarcoma – a malignant tumour formed of connective tissue cells - proved an especially interesting research emphasis, since this disease can arise following injections or vaccination (vaccine-associated or «injection-site» sarcoma). For this reason we wanted to avoid mistletoe injections and instead used an oral mistletoe preparation (Viscum quercus praeparatum 0.1% Dilaq). The outcome of the study successfully established use of oral mistletoe therapy since relapse-free periods for cats increased after surgical removal of the nodule [(1)]. In addition, an expert report enabled us to gain retrospective registration of Viscum quercus praeparatum in 0.1% solution.

For dogs, teat tumours are a challenge in daily veterinary practice due to their frequency and usually poor prognosis. A controlled study on Iscador therapy was started in collaboration with Justus-Liebig University (KGGA) in 2008. The findings of the study are of particular importance since hitherto there has been no evidence of successful adjuvant therapy standards (radiotherapy, chemo- and hormone therapy) for female dogs following removal of teat tumours. Evaluations of the study demonstrated a trend towards roughly 75% reduction in mortality risks for the dogs who were given supplementary treatment with Iscador following surgery. A further aspect of the study was the recording of quality of life for pets given mistletoe treatment, something not previously established or validated in veterinary medicine for animals suffering from cancer. Using a newly conceived questionnaire, activity, appetite, pain, and general quality of life were ascertained. Female dogs receiving post-operative mistletoe therapy showed a highly stable quality of life even at an advanced age.

A retrospective study on adjuvant mistletoe therapy following surgery and/or radiotherapy of dogs with oral melanoma (highly malignant tumours in the oral cavity with strong tendency to metastasis) was undertaken at a veterinary oncology centre (Animal Oncology and Imaging Center, Hünenberg). Evaluations on oral melanoma have now been concluded, and show very promising results. Publication is envisaged for 2017.

Mistletoe therapy for horses

The primary focus in relation to horses was treatment of equine sarcoid (the most common type of skin tumour). A randomized, placebo-controlled study on the action and efficacy of Iscador therapy was undertaken, and a significantly increased rate for cure and improvement of sarcoids was ascertained in the mistletoe group [(2)]. A follow-up study of the horses five years after the start of mistle-

Large and small patients of U. Biegel. Photo: O. Christen

Dr. Christen surrounded by her patients. Photo: U. Biegel

toe therapy showed still greater success: after one year the chance of a cure following Iscador treatment was three times greater, and after five years eight times greater than from placebo treatment [3].

Since 2007, extensive case documentations have been drawn up on Iscador treatment of over 150 horses and donkeys with equine sarcoid. Currently these data are being analysed to determine how best to optimize the therapy protocol to increase cure rates in recidivating conditions and in therapy-resistant horses.

Conferences on animal mistletoe therapy

In order to increase our knowledge and understanding of mistletoe therapy in veterinary medicine, the idea arose to bring together vets with experience in using Iscador. The first international Viscumvet meeting took place in Dornach in 2001. Thereafter, an ongoing series of gatherings took place in various places (Dornach, Frick, Arlesheim, Avenches, Paris). Invited participants were veterinary oncologists, mistletoe experts and users (veterinary and human medicine), manufacturers and advisers from Germany, Austria, Switzerland, France, Brazil and Sweden. At least partly arising from these exchanges, an internet platform was developed (www.viscumvet.org) where livestock owners, therapists and vets can find detailed information. A password-protected portal for vets was established to make available the various treatment protocols and specific information on choice of mistletoe varieties or preparation types.

Through international lecturing activities undertaken by the Viscumvet group, and their participation in further and advanced training courses in practical veterinary medicine, mistletoe therapy is now meeting with growing interest, and the number of users is increasing. Mistletoe therapy is now, for instance, a firm part of the further training courses in veterinary medicine, run by the Swiss Medical Association for Phytotherapy (SMGP), which lead to the award of a certificate in veterinary phytotherapy from the Association of Swiss Vets (GST).

Research work and veterinary practice by vets in the Viscumvet group goes hand in hand with, and mutually benefits, the advisory work with vets, therapists and livestock owners. Close supervision of mistletoe therapy patients and users helps vets school and refine their observations of treatment progressions, and the effects of mistletoe. This means that treatment protocols can be optimized and verified through controlled clinical trials.

Outlook for mistletoe research at the Research Institute for Organic Agriculture

Forthcoming treatment emphases for small animals will be on very malignant tumours, especially in dogs, that prove difficult to treat. Mistletoe therapy could be helpful in such cases. They include osteosarcoma (malignant bone tumours) which are very common in large dog types (e.g. Irish Wolfhound, Greyhound, Rottweiler, Great Danes etc.), and not infrequently metastize despite surgery. Metastasis-inhibiting action needs to be studied, as do prophylactic measures with mistletoe treatment for dog species at risk.

Only 10% of dogs (30% with chemotherapy) survive for one year with hemangioma, and this low survival rate is a big problem. In some instances, mistletoe therapy has proven effective in inhibiting relapse or metastasis. Verifying this would be another important research goal.

Extending and validating the available questionnaire on quality of life for dogs, would be another innovative research project, since, above and beyond mistletoe therapy itself, this is of importance for assessing a variety of treatment methods. It could serve appraisal in veterinary medicine of the phenomenon of «fatigue» well-known in human medicine. As in human beings, it becomes apparent that dogs receiving mistletoe therapy are more lively and active.

In relation to horses, it would be interesting to study oral administration of mistletoe, since horse owners have often been disinclined to give frequent mistletoe injections, instead preferring to administer it by mouth; and this has shown some success. However, sarcoids appear to take longer to heal by this method. A study began in 2017 to investigate the potential of this type of usage.

Another research emphasis in horses is on tolerance and efficacy of the lime substance of mistletoe in clinical use, either as ointment or through injection of the emulsion.

And finally, mistletoe is also being used increasingly for treating other equine tumours such as melanomas, lymphomas, mastocyte tumours and plate epithelial carcinomas, with a view to future studies.

The Viscumvet group also receives enquiries on treating tumours (therapy protocol, tolerance, efficacy) in cows, goats, rats, rabbits, mice, ferrets, and also birds (chiefly parrots and parakeets). In some cases mistletoe treatment also appears to be effective here, thus opening up a further field for potential future research. ■

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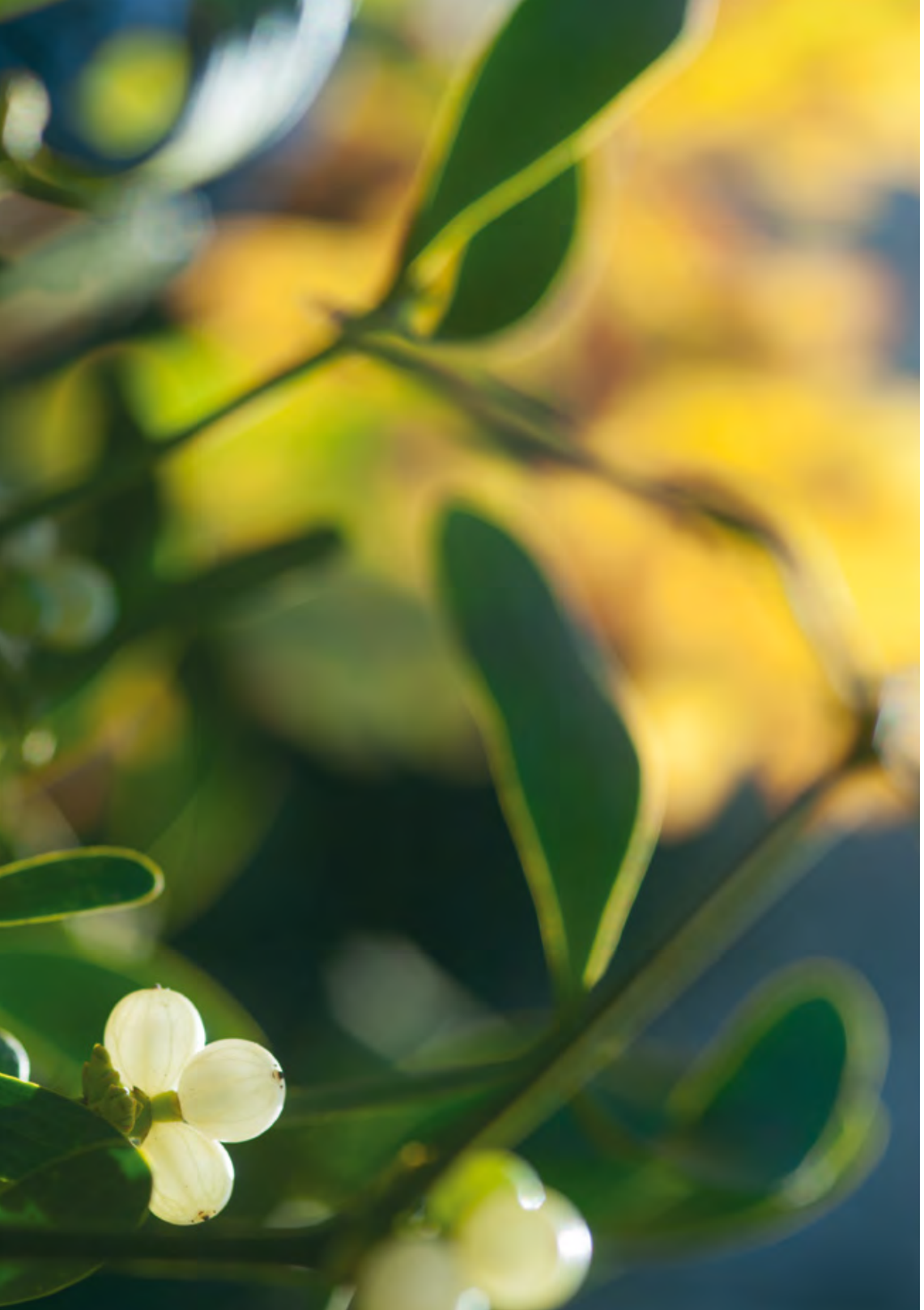

Progress in understanding the mechanisms that support the use of European Viscum album as complementary therapy in cancer

MRINMOY DAS, DR. JAGADEESH BAYRY, PROF. DR. SRINI V. KAVERI

European mistletoe (*Viscum album L.*) is a semi-parasitic evergreen shrub that grows on a number of host trees. It is a traditional phytomedicine of Europe, commonly known as European mistletoe, also found in Western and Southern Asia. Medicinal uses of mistletoe are recorded for hypertension, anxiety, insomnia, headache, internal bleeding and arteriosclerosis. It has been used as a sole intervention or as complement to the conventional cancer therapies. Mistletoe treatment is beneficial for cancer patients in terms of survival, improved quality of life and reducing the side effects of conventional anticancer therapies. It also exhibits multifarious biological activities including anti-inflammatory, immunomodulatory, anti-oxidant, cytotoxic, anti-angiogenic, anti-hypertensive and anti-diabetic functions.

The pharmacological components of European mistletoe are lectins, viscotoxins, polysaccharides, glycoproteins, peptides, amines, triterpenes, alkaloids, lipids, cyclitols, vesicles and flavonoids. Several preparations of mistletoe are available for the therapy. Each mistletoe preparation is different because of its chemical composition, which varies depending on the time of harvest, species of host tree and preparation methods; together these factors influence considerably the clinical efficacy of mistletoe. Recently, a comparative study of five different preparations of mistletoe (Iscador Qu spez, Iscador Qu Frf, Iscador M spez, Iscador P and Iscador A) has shown that Iscador Qu spez is the most potent preparation in activating human dendritic cells and promoting Th1 response [(1)]. Apart from its anti-tumor properties, Iscador

Qu spez employs a novel anti-inflammatory effect by selectively downregulating the cyclooxygenase-2 (COX-2) mediated cytokine-induced secretion of prostaglandin E2 (PGE2) via destabilization of cox-2 mRNA [2].

Cancer fatigue is one of the main symptoms that significantly affect the quality of life of patients. Cancer-related fatigue may be related to both the disease process and treatments, including surgery, chemotherapy and radiation therapy. Factors contributing to fatigue include anemia, weight loss, fever, pain, medication and infection. Recently, in non-metastatic colorectal cancer, the use of mistletoe preparations has shown improvement of cancer-related fatigue in a randomized clinical trial [3]. The exact reason for cancer fatigue is unknown. Some of the proposed mechanisms underlying cancer-related fatigue includes alternations in muscle and ATP metabolism and cytokine dysregulation.

Recently, several studies have been focused on anti-fatigue activity of mistletoe. Cancer and its treatment (chemotherapy, surgery, radiotherapy, and biologic therapies) are associated with increase in the prevalence of fatigue and in the plasma levels of inflammatory cytokines, especially TNF-α, IL-1β, and IL-6. Cytokine antagonists have promise for reducing cancer-related fatigue in cancer patients. Further, several studies have shown that chemotherapy treatment induces cellular stress response. Cellular stress that activates globally endoplasmic reticulum stress can cause muscle atrophy. Recent studies have shown that Korean mistletoe extract increase mitochondrial activity. In the treadmill and swimming tests, mice treated with Korean mistletoe extract showed increased exercise capacity, indicating its beneficial functions in enhancing the capacity of skeletal muscle [4]. Further, Korean mistletoe extract showed inhibitory effects on muscle atrophy and positive regulatory effects of the maintenance of muscle mass [5]. These emerging evidences form a platform for further experimental studies and controlled prospective clinical trials to improve cancer-related fatigue and quality of life in cancer patients. Also, molecular dissection is necessary in order to understand anti-fatigue activity of mistletoe. ■

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Case reports in mistletoe therapy research

DR. PAUL G. WERTHMANN, DR. GUNVER S. KIENLE, DR. HELMUT KIENE

«Case reports … cornerstones of medical progress»

Jan P. Vandenbroucke, Epidemiologist

Case reports – the description of, for example, therapy and treatment results in individual patients – are one of the oldest means of recording and passing on medical experiences. The Ebers Papyrus described case histories in Egypt over three thousand years ago. Case reports have always contributed significantly to understanding of and knowledge about illness, diagnosis and therapies. Today more than 50'000 case reports are published in medical journals each year.

In a clinical study a specific question of patient care is looked at precisely, but in isolation, as if through a keyhole; a case report, in contrast, offers insight into all aspects of the patient's treatment. Judgements formed in relation to the specific individual case and the professional consequences of actions can be understood – and learned by others. New treatment methods can be presented with their rationale, and special adaptations for specific patients and situations, so that the reader is introduced to the method's overall process. Observations in the individual case can be described in detail.

Case reports are appropriate particularly where complex interconnections are to be discussed. They form a large part of the publications in the field of paediatric surgery. But in the field of cardiology, too, with its many studies, almost half the guidelines are based on case reports, expert opinions and the health provision standards.[1]

Case reports can be written by every practising physician with comparatively little effort and are greatly valued by the physicians reading them. Physicians recognize much in the descriptions and can easily follow them – this could be their next patient.

Case reports on cancer patients treated with mistletoe therapy

The following examples are intended to show how case reports contribute significantly to the research into, and further development of mistletoe therapy:

The start of mistletoe therapy – treatment pauses and fever

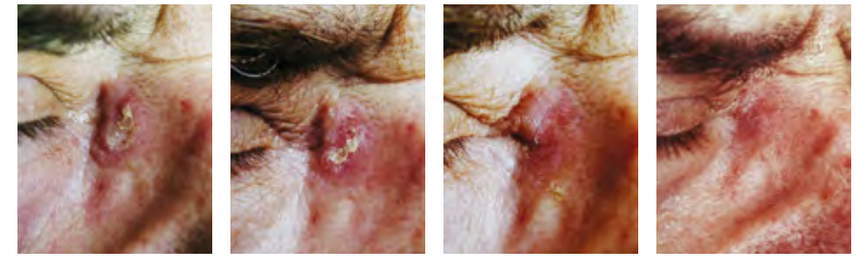
From the first treatments in 1917 onwards, Ita Wegman repeatedly described the case histories of patients treated with mistletoe preparations and also asked all colleagues using these preparations for similar reports. In order to optimize the treatment, the experiences of individual physicians were thus shared with other physicians who also gained their own experiences with the preparations. In 1927 Ita Wegman described a patient with a tumour in the pylorus region in whom the complaints clearly improved and the previously palpable tumour was no longer palpable: «Characteristic for the treatment of this patient is that initially at every attempt to pause the injections for several weeks or months, and subsequently in a pause of several months, a deterioration kept occurring which made renewed treatment necessary. Furthermore, it is worthy of note here that acute febrile states, once they had been overcome, always meant progress in the return to health of the patient. (a)»

What aspects should be considered in choosing the mistletoe preparation?

Mistletoe therapy is mostly geared very specifically to the individual patient. In doing so, physicians have gathered a lot of experience in the choice of preparations. Markus Sommer and Georg Soldner showed through case reports how they chose the mistletoe preparation on the basis of specific characteristics of the patient and tumour. Alongside the further considerations in this article, such case reports are precisely what offer explicit insight into the wealth of experience of physicians, and make it accessible to other colleagues: «(...) With a strong constitution and the pugnacious willingness to overcome her tumour in order to lead a fulfilled life, we chose the relatively cytotoxic mistletoe from apple trees for the patient, in a higher dosage that clearly contributed to her very pleasing progress. (b)»

Case reports on local mistletoe injections

Alongside the choice of preparations, the way that they were used also became increasingly specific – preparations which were initially mainly injected subcutaneously were joined by other methods of administration. In 1978 Professor Salzer from Vienna reported on a series of cases



a) b) c) d)

Picture 1: A squamous cell carcinoma was injected with mistletoe. a) shows the whole tumour; b)-d) were taken at intervals of 2½ months each.
[From: Phytomedicine, Volume 20, Issues 3–4, Paul G Werthmann, Gregor Sträter, Hedda Friesland, Gunver S Kienle, Durable response of cutaneous squamous cell carcinoma following high-dose peri-lesional injections of Viscum album extracts – A case report, Page 325, copyright (2013), with kind permission of Elsevier]

in which mistletoe extract was injected into the pleura, where fluid had collected as a result of cancer. He described several cases of patients in which the water collecting in the pleura was reduced through mistletoe treatment (c). Today the injection of mistletoe preparations into the pleura is carried out in several clinics, often with conglutination of the pleura or even regression of the tumour. Even in a clinical picture in which children were born with fluid collecting in the pleural cavity, a mistletoe preparation was successfully injected (d).

Case report on treatment close to the tumour

The injection site of the mistletoe preparation was also debated to further optimize treatment. In 1996 Armin Scheffler published a case report in the International journal of Oral and Maxillofacial Surgery in which the patient was given mistletoe treatment as a direct injection into the tumour. This treatment led to severe inflammation and a complete regression of the tumour (e). Encouraged by this report, other physicians also started to treat tumours with mistletoe injections near or into the tumour – often with good results. Werthmann reported on two patients: in one, a squamous cell carcinoma was injected with mistletoe and regression occurred (see picture 1); in the other report, a tumour in the minor salivary glands at the gum (adenoid cystic carcinoma) encapsulated itself and reduced in size (f, g).

Case report on the administration of high dosages of mistletoe

In which dosage does mistletoe therapy show itself to be most effective? While the manufacturers tend to recommend lower dosages, some physicians have had good experiences with higher-dosage preparations – and published them as case reports: Maurice Orange treated patients with various types of cancer (breast cancer, Merkel cell carcinoma, lymphoma)

with high-dosage mistletoe therapy, using injections into the tumour, subcutaneous mistletoe injections, as well as mistletoe infusions. This high-dosage treatment led to the complete regression of the cancers (h, i).

Case report on cancer fatigue

Alongside tumour-associated changes, many concomitant disorders play a crucial – often life-determining – role in cancer patients, and here too variations between different treatments can be recorded. Chronic fatigue syndrome, «cancer fatigue», is a phenomenon from which many cancer patients suffer and which brings with it considerable restrictions in quality of life: long-term fatigue develops which cannot be offset by sleep. In 2009 Kathrin Wode from Sweden published a case report in which a clear improvement in cancer fatigue could be observed as the result of mistletoe therapy. What was familiar from some studies as «improvement in quality of life», could be traced here in detailed form (j).

Professionalization of case reports and their contribution to medical science

Case reports can contribute much to practice and further research – but only if the reports are of sufficient quality. In 2013 the consensus-based CARE Guideline was drawn up and published by an international team of researchers, providing guidelines for the completeness and quality of case reports [(2)].

The individual patient as a source of knowledge is often evident to the practising physician. But in today's statistically oriented medical research the possibility of valid knowledge being obtained from the individual is seen as unlikely and has not been pursued further. There have, however, been new developments in recent years. The subject of individual enhancement of knowledge via the single case has been investigated in detail, and has shown a broad spectrum of methodological possibilities for identifying cause-effect relationships in the treatment of the individual patient [(3)]. Case reports therefore contain great future potential so that Milos Jenicek, a co-founder of Evidence-Based Medicine recently wrote: «… the future of clinical case reporting in all health sciences is bright.» [(4)]. ■

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Mistletoe cultivation – pioneering spirit and constant challenge

DR. HARTMUT RAMM

Background

A central concern of the botany department of the Society for Cancer Research is the cultivation of mistletoe on tree species on which it rarely grows in nature. The practical work started soon after the establishment of the Hiscia Institute in 1949 when Paul-Heinz Bellmann took on the task of cultivating mistletoe on indigenous oak trees. Until then no one had succeeded in doing so. However, the history of this endeavour goes back a lot further. In 1917 Ita Wegman had the first mistletoe preparation made from the easily available apple-tree mistletoe; but the wish soon arose also to use rare oak mistletoe after Rudolf Steiner recommended, three years later, that the various qualities of mistletoe, depending on the host tree, should be taken into account depending on the patient and type of tumour. Because oak mistletoe was not easily available, it was initially replaced by the distantly related hornbeam. Then, in 1923, Karl von Tubeuf in his «Monograph on Mistletoe» documented the mistletoe oak tree at Isigny-le-Buat from where Ita Wegman and her staff immediately had oak mistletoe sent for making the preparation Iscador Qu. In 1949 staff from the Hiscia Institute for the first time themselves harvested mistletoe from this oak and as Q1 (Q = Quercus = Oak) used it to start the mistletoe oak archive of the Society for Cancer Research, which has been continually extended and updated to the present day. Through decades of targeted search activities by staff from the Hiscia Institute, about 400 mistletoe-bearing oak tree locations have been identified in the wild in France. But only a small number of them bear enough mistletoe bushes for a sustainable harvest.

Four decades of oak mistletoe cultivation

With hindsight it turns out to have been a wise decision for those responsible at the Society for Cancer Research to establish the early goal of cultivating white-berried mistletoe (*Viscum album*) on common and sessile oak (Quercus robur/petraea). It was a sobering fact that only one oak in Arlesheim actually bore mistletoe after 12 project years and 15'000 sown mistletoe seeds, but it showed at the same time that the cultivation of mistletoe on oak was not absolutely impossible. The breakthrough occurred in 1976 when Gianfranco Grazi identified the genetic disposition of mistletoe-bearing

Mistletoe-bearing oak trees in France.
Photos by Konrad Urech (right)
and Jürg Buess (above).

Final location with sown acorns (left); young oaks almost two decades after having been sown (right). Photos: H. Ramm

oak trees and postulated that it should be possible to transfer the receptivity for mistletoe of these oaks to their descendants. Grazi soon succeeded in confirming this genetic hypothesis on grafted mistletoe oaks and then in increasing this stock with seeds from French mistletoe oaks through generative propagation. We subsequently moved the sowing and testing of the young oaks from the tree nursery to the respective final locations in order to protect the typical tap root of oaks through direct sowing.

After four decades of oak mistletoe cultivation, we now have almost 400 young mistletoe-bearing oaks on about 12 hectares at eleven of our locations in Germany, France and Switzerland. Although the trees are still relatively young, we can meanwhile cover not just the whole oak-mistletoe berry harvest from the stock under cultivation but also an increasingly large proportion of the plant harvest for the production of Iscador Qu.

But both mistletoe and oak grow slowly. That is why we have to plan now already for the requirements in 10 to 20 years. Furthermore, the bigger it grows, mistletoe is increasingly at risk of damage from snow and wind, late frost and biotic harm. These uncertainties will continue to rise as the variations in climate increase. In cultivating oak mistletoe, we are therefore continuously working to obtain a surplus but at the same time set ourselves the task of supporting the vitality of the mother trees. Thus the management of the sites was improved in recent years through thinning the stock of trees, and the use of biodynamic preparations was introduced. But growing stocks of oak mistletoe will in future also allow us to develop ever greater quality enhancement measures such as a more specific selection and boosting of vigorous mistletoe bushes, but also targeted intervention analogous to the pruning of fruit trees, to allow both the oak and mistletoe to grow healthily.

Elm mistletoe at risk

The vulnerability of mistletoe cultivation can be seen in the elm mistletoe. In 1952 Hiscia staff discovered the first mistletoe-bearing elms in France and soon afterwards the physicians could be pro-

Three-year-old mistletoe on oak (above) and a roughly 30-year-old cultivated mistletoe oak (left).
Photos: H. Ramm

Mistletoe cultivation at the edge of land in agricultural use: a cultivated mistletoe elm with various mistletoe bushes in a hedge alongside a line of oaks potentially capable of receiving mistletoe (left picture). Six years after being sown, the mistletoe bushes on the blossoming elm will soon be big enough to harvest (right picture). Photos: H. Ramm

vided with the elm mistletoe preparation Iscador U. Over the years dozens more mistletoe elms were found primarily in France which in addition could easily be propagated through root cuttings. From 1990 onwards the demand for elm mistletoe could be completely covered from cultivated stocks. This was all the more important as in the meantime Dutch elm disease, rampant throughout Europe, had largely killed off the harvest-ready wild stocks of elm mistletoe. In 2007, Dutch elm disease also began to affect the cultivated sites where meanwhile more than 90 percent of mistletoe-bearing elms have died. Enough mistletoe is still growing on the surviving elms to cover the current demand for Iscador U. We are protecting these older mistletoe elms through more intensified tree hygiene and are strengthening them through additional measures such as biodynamic preparations.

In order to secure the long-term supply of elm mistletoe, we are regularly growing young trees from the seeds of vigorous mistletoe elms and are planting these young elms, which have been tested for their mistletoe receptivity, at various locations. Our short-term goal consists of making young mistletoe elms ready for harvest more quickly as older mistletoe elms fall victim to Dutch elm disease. Because it will soon be possible to harvest the first mistletoe on some of the young elms, of which there are now well over 100, we class the supply of elm mistletoe as secure in the medium term. But our goal is to find trees among these generatively propagated mistletoe elms which are resilient or indeed exhibit a sufficient level of resistance against Dutch elm disease.

New challenges

New phenomena such as ash dieback sharpen our alertness for diseases in trees on which we cultivate mistletoe for the production of Iscador. It is already becoming apparent that in the medium term even the stocks of apple tree mistletoe, of which there have been plenty until now, might be under threat. Because the new leaf disease known as Marssonina is very difficult to control by biological means and the demand for mistletoe from apple trees is very great, measures must now already be considered so that patients have an assured supply of Iscador M also 20 years hence. Alongside the planting of resistant apple species, such measures also include moving cultivation sites to regions which have not yet been affected by this new disease.

Having gained a lot of experience in recent decades in the propagation of mistletoe oaks through grafting, tree nurseries and direct sowing, we want in the future to continue to develop the cross-pollination of mistletoe-bearing oaks for harvesting. First experiments set up by Gianfranco Grazi as long ago as 1985 produced promising results in generative propagation in that the proportion of mistletoe-receptive descendants almost doubled.

Lastly, by planting all Iscador host tree species on as many of our eleven sites as possible, we want to create the basis for future generations of researchers to access mistletoe samples optimally comparable with regard to host tree, soil and climate, so that they can study the substances they contain and their therapeutic potential. ■

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Methods of clinical research

DR. WILFRIED TRÖGER

Clinical research is used to verify the efficacy, safety and cost effectiveness of medicines, as well as of therapeutic and preventive measures, and measures to maintain health. This definition extends to three areas: identifying medicines, safety of medicines and the cost of medicines. Research in these areas must use different methods to obtain meaningful results. In addition, ethical principles must be observed.

The individual and unique meeting between the patient and their physician or therapist is the source of effective treatment. Hence prospective analysis in each case is the adequate method to show efficacy because it confirms or disproves the hypothesis formulated in advance by the physician [1]. For proof of safety, the retrospective study determines side effects after the event. Comparative studies must be undertaken to show cost effectiveness.

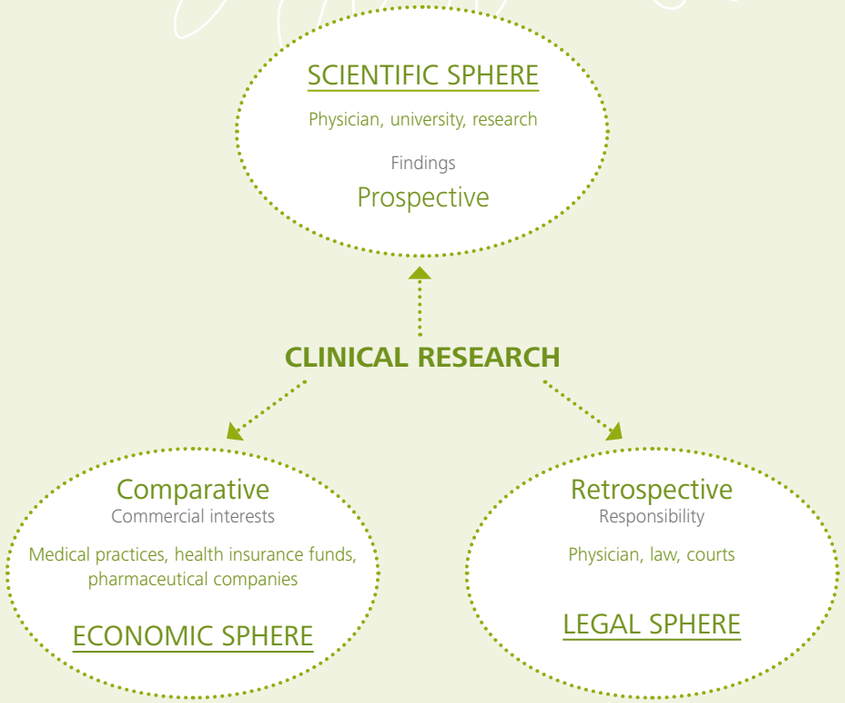
In the first area, proof of efficacy, there are restrictions today because certain paradigms govern the predominant scientific view.

- Materialism proceeds on the assumption that no holistic, formative, shaping forces exist. The consequence of this is, among other things, that in principle all medicines are standardized by their ingredients, and that potentized medicines have lost their legitimacy.

- Darwinism proceeds on the assumption that there are no higher-order relationships governed by laws. The consequence is that, for example, the rationale for the use of anthroposophic medicines has disappeared and homoeopathy has to relinquish the simile principle.

- Statistics become necessary because insight into cause and effect in each individual case is abandoned, since it appears too complex. This means that the individual approach to treatment is lost.

These restrictions on what is ideologically acceptable in society means that the prospective single case study is deemed to be unsuitable for proof of efficacy. Instead the prospective randomized double blind study is required, which actually has its origins in the economic sphere. Through comparative statistics and double blinding of studies (the physician does not know what they are prescribing and the patient does not know what they are being given) clinical studies fundamentally lose sight of the patient and physician: the medicament itself is the absolute focus. The individual judgement of the patient and physician even tends to be seen as disruptive and is eliminated from research as much as possible. A statistically significant difference between two patient groups is sufficient for the licensing of the medicine which can then be granted in principle without individual insight into cause and effect.



Structure of the clinical research requirements.

Single-case documentation does not occupy the position in licensing and medicine which it really should. Hence so-called «unconventional therapeutic methods» (which include anthroposophic medicine) also have to be tested with study methods which unfortunately take no account of the individual needs of the patient.

Nevertheless, the number of published single-case reports per year has doubled between 2005 and 2016 and has caught up with published studies [2]. The anthroposophic medical approach asserts that it can make a substantial contribution to insight into cause and effect, and an instructive single case encourages us to adopt the ideas (hypotheses) and procedure (method) of the reporting physician. That does, however, require all therapies and their successful use to be well described. Hence the CARE Guidelines [3] introduced since 2013 provide instructions for single-case documentation and are a requirement for publication.

From the perspective of cancer research, carefully documented single-case studies on mistletoe therapy are essential. For this reason we are collaborating with physicians and therapists to draft and publish single cases. ■

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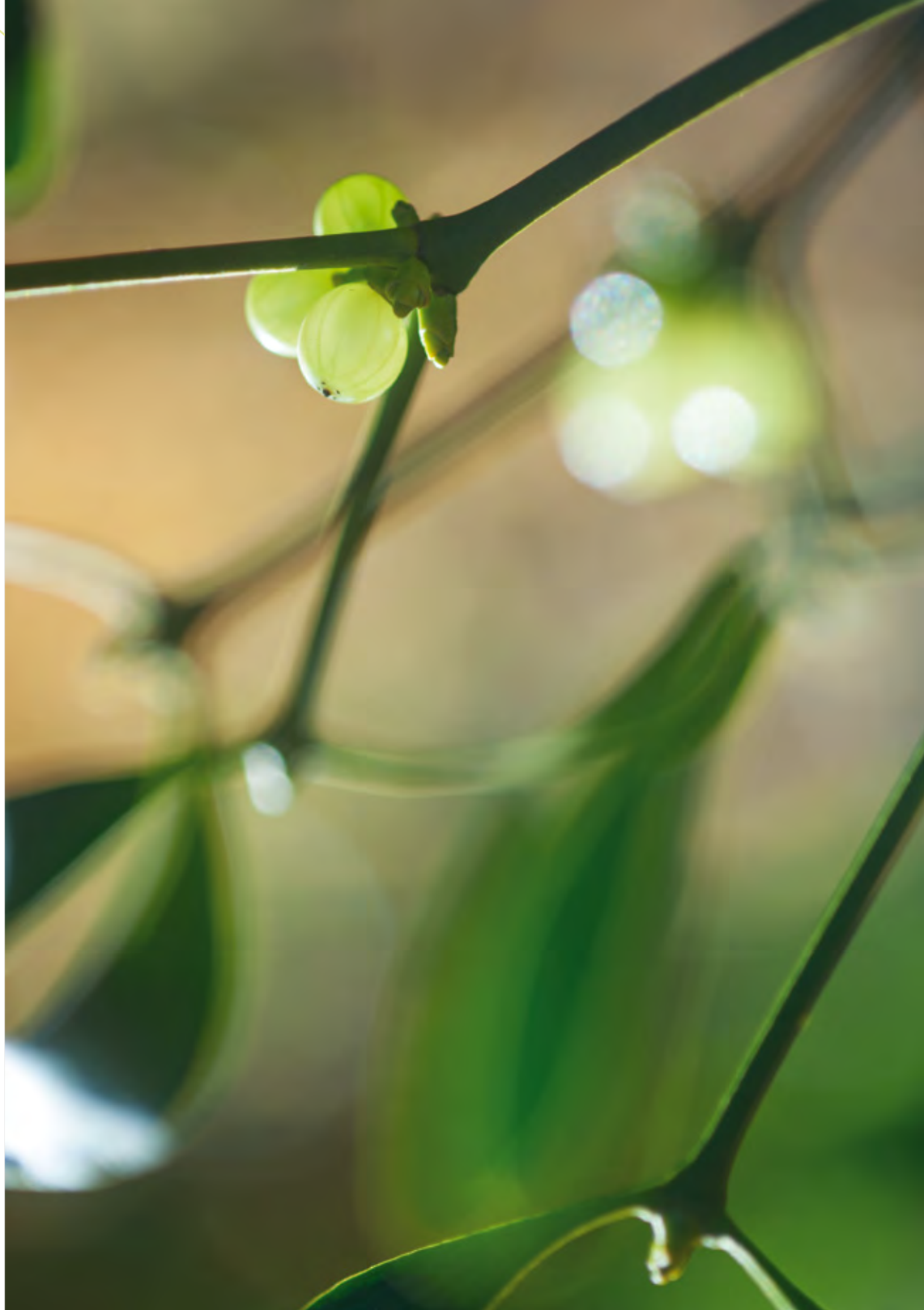


Picture-forming methods: mistletoe and host-tree qualities in circular chromatograms

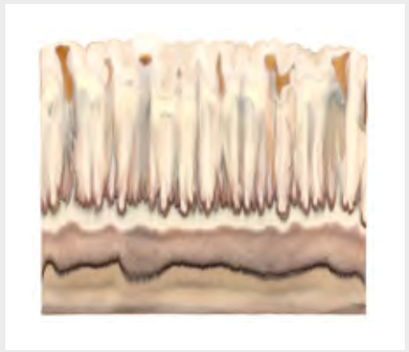
DR. CLAUDIA SCHERR

The white berried mistletoe (*Viscum album L.*) occurs in Europe in three subspecies: fir mistletoe (*Viscum album* ssp. *abietis*) grows exclusively on firs, pine mistletoe (*Viscum album* ssp. *austriacum*) on pines, while deciduous mistletoe (*Viscum album* ssp. *album*) can be found on various species of deciduous trees such as apple trees, oak or elm. Mistletoe and its associated host trees form a close biotic community in which the mistletoe absorbs those substances which the tree provides through its open vascular bundles. These substances are required for the formation, among other things, of the mistletoe's own typical toxic substances such as mistletoe lectin and viscotoxin. Mistletoe is thus directly connected with the life or formative forces of the tree [(1)]. The life forces taken from the host tree are of key significance for the efficacy of mistletoe in cancer treatment, according to Rudolf Steiner.

In preparing the anthroposophic mistletoe preparations for cancer therapy, these differences are taken into account and the mistletoe is harvested and processed strictly by host tree. In total, anthroposophic mistletoe preparations are available from 13 different host trees.

«Picture-forming methods» offer one way of researching and describing host-tree qualities in mistletoe preparations. These methods originated with the experiments of Lili Kolisko. In 1923 she studied the formative forces of plants by dripping extracts of plant sap on filter paper as suggested by Rudolf Steiner, letting it rise in accordance with the principle of capillary dynamolysis, and analysed the resulting forms. These forms became more clearly differentiated if she added metal salt solutions (silver nitrate, gold chloride, iron sulphate, copper sulphate and others) to the rising picture [(2)].

Today we distinguish between the following classic picture-forming methods: rising picture mehod (capillary dynamolysis), circular filter chromatography, copper chloride crystallization and drop-picture method (Fig 1). Then there are more recent methods such as the droplet evaporation method (see article by M. O. Kokornaczyk). Picture-forming methods are used largely in an anthroposophic context for quality analyses in the fields of agriculture, pharmacy and medicine. All the methods can be used to study liquid samples (such as plant extracts, blood, water); the result is «pictures» dependent on concentra-



Capillary dynamolysis method as developed by WALA (1a)

Circular chromatography as developed by Hiscia (1b)

Circular chromatography as developed by Pfeiffer (1c)

Copper chloride crystallization as developed by Pfeiffer (1d)

Drop picture method as developed by Schwenk (1e)

Fig.1 : Iscador M spez, analysed using the capillary dynamolysis method as developed by WALA (1a), circular chromatography as developed by Hiscia (1b), circular chromatography as developed by Pfeiffer (1c), copper chloride crystallization as developed by Pfeiffer (1d) (Photos: J. Fritz) *as well as Iscador P analysed with the drop-picture method as developed by Schwenk (1e)* (Photo: C. Sutter)

tion and specific to each sample which are analysed in a qualitative comparison. Which method is used depends, on the one hand, on the quality of the sample to be analysed and, on the other, on the questions under investigation. The methods also complement one another – analysing a sample using several picture-forming methods can therefore be very illuminating.

Picture-forming methods can also be used to complement modern scientific analysis methods which today allow for a subtle differentiation of the material composition of mistletoe samples from various host trees. Undoubtedly the material composition also contributes to configuring the picture. But the real strength of picture-forming methods lies in their ability to help bring to expression the formative capacities of the plant sap, which in turn is related to the formative forces of the whole plant. These formative forces serve to give and preserve the shape of the plant. Hence, in analysing the pictures, particular attention is also paid to the forms that arise.

Picture-forming methods have been used for many decades at the Hiscia Institute for extending quality assurance in the manufacturing process of Iscador and for other specific research questions. For 25 years Agnes Fyfe made daily pictures of fresh plant extracts from mistletoe shoots using capillary dynamolysis, and correlated the forms with planetary constellations to identify cosmic rhythms, thus determining optimal harvest times [3]. Heidi Flückiger has particularly studied host trees and the differentiation of the individual Iscador varieties [4, 5]. The author is now continuing this work.

Circular chromatography, in which the liquids spread horizontally on the filter paper, is particularly suitable for investigating the qualities of host trees. The paper is impregnated with silver nitrate for this purpose. Once the silver nitrate has dried, the plant sap, which has been mixed with sodium hydroxide solution, is then made to flow on the paper. The sap which has thus been solubilized flows through the silver nitrate front, and the characteristic form and colour appear on the picture. A few days later the pictures are fully developed and can be analysed. For a direct comparison of the saps it is important that the pictures are developed at the same time since pictures made at different times frequently differ slightly. But with sufficient experience these pictures can also be correctly assigned to the host trees.

As set out in Flückiger [5], the pictures from the green host-tree leaves shortly before taking on their autumn colours are dense and compact. With the onset of autumn colours, the pictures open up again, showing more clearly than at any other time of the year the characteristic features of the plants being studied. Hence it is at this season that we compare and juxtapose the circular pictures from the fresh sap of the autumn leaf of the host tree, the mistletoe leaf, and the corresponding Iscador variety.

To begin with, it can be seen on the circular pictures shown in Fig. 2 that different mistletoe subspecies, but also the various

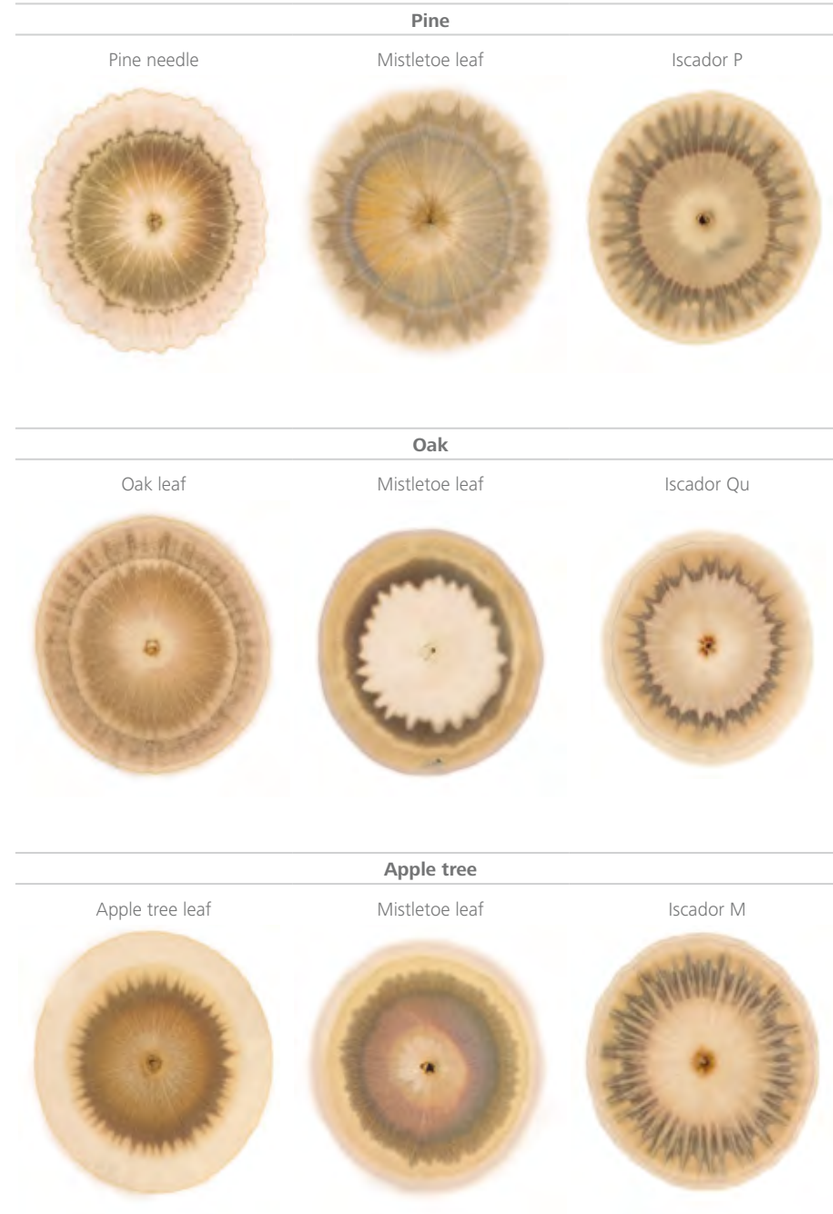


Fig. 2: circular pictures of the fresh saps of a needle or autumn leaf from a host tree, the mistletoe leaf and the corresponding Iscador variety, shown for the three host tree groups pine, oak, apple (Photos: J. Buess)

deciduous mistletoes, can easily be distinguished from one another through circular chromatography. If we let the pictures act on us for a while, commonalities within the host tree groups become apparent: a peripherally oriented, colourful shape with a variety of forms is characteristic of the pine group. The oak group has powerful forms with a clearly apparent core zone. The apple tree group displays a rather restrained but at the same time strongly radiating shape. We can thus see related characteristics in the pictures of the host tree leaves and those of the corresponding Iscador variety. It seems that the mistletoe fermentation process in the production of Iscador allows the quality of the host tree to come more clearly to expression.

This phenomenon can be seen as coinciding with Rudolf Steiner's requirement that the mistletoe should be processed in such a way that it can transfer the etheric component it has taken from the host tree to the human being (6). In future this question will be studied further, and the Iscador machine process studied in greater detail using picture-forming methods. ■

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The Oncology Network in 2017 – evaluation of integrative oncology treatment concepts in daily healthcare provision

DR. ANJA THRONICKE, ANTJE MERKLE , DR. FRIEDEMANN SCHAD

The concepts of integrative oncology, as these have been used by anthroposophic medicine for decades, are gaining increasing importance and recognition. The treatment concepts of integrative oncology involve combining modern medical provision with complementary anthroposophic therapies and psycho-oncological care.

Despite its widespread use, integrative oncology in clinical practice has not so far been the subject of much scientific study. Nor do integrative oncological therapies figure in classical cancer registers. In 2005, therefore, a clinical register was established under the name of the «Oncology Network», with the aim of documenting not only standard tumour treatments but especially also mistletoe therapy and other complementary anthroposophic integrative therapies – such as psycho-oncological care, artistic therapies, external applications and eurythmy therapy in daily clinical provision [1]. At the same time, the network systematically records patients' quality of life in after-care provision. In November 2016, the register was officially accredited as a study by the German Cancer Association (www.studybox.de/search).

At the 32nd German Cancer Congress in Berlin (2016), research into healthcare provision was designated a key element in modern oncology in respect of the long-term evaluation of factors affecting patients. With this in mind, systematic research is being undertaken within the Oncology Network into implementation of anthroposophic therapies under everyday clinical conditions. The long-term aim of the Oncology Network project is to develop anthroposophically-oriented oncology and achieve qualitative improvement in the care of tumour patients.

The data analysed from the Oncology Network register are intended, for instance, to help answer the following questions:

1. Why do patients receive mistletoe therapy?
2. How many patients participating in the Oncology Network receive mistletoe therapy?
3. How safe is mistletoe therapy?
4. How effective is mistletoe therapy?
5. How does mistletoe therapy affect quality of life?

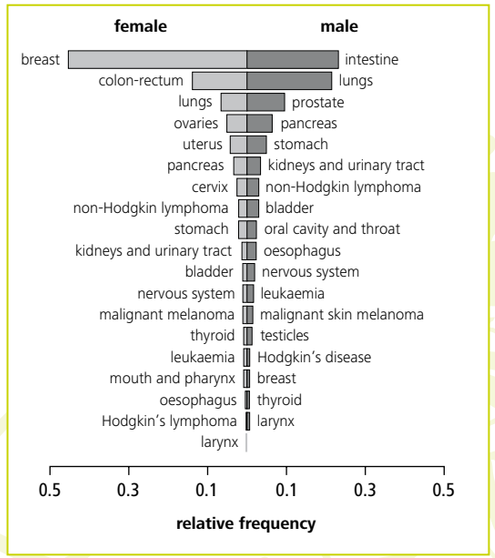

Diagram 1. Relative frequency of tumour entities in male and female cancer patients in the Oncology Network register

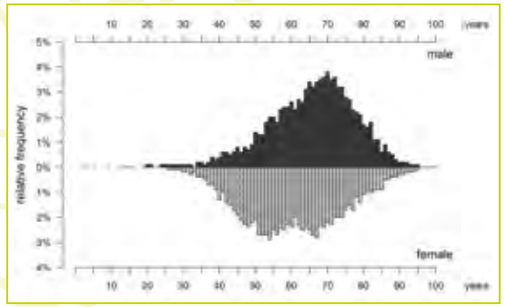

Diagram 2. Age distribution of patients registered in the Oncology Network, classified by gender. As at 30 June 2016.

The documentation is being undertaken at clinics with oncology emphases and in oncology practices with an integrative, anthroposophic orientation. It includes male and female cancer patients aged between 18 and 100. Since 2005, over 15,900 cancer patients were registered in the Oncology Network (as at 30 June 2016).

In 2013 an initial analysis was done of recorded patients and their tumour-related therapies [1]. As regards the type of tumour, and age and sex of the patient, distribution in the Oncology Network only slightly differs from that of other, conventional cancer registries (diagram 1, diagram 2). Thus it was apparent that a disproportionately high number of young women with breast cancer are registered in the Oncology Network, reflecting their desire to be treated in an integrative oncology context.

The commonest types of cancer in women in the Oncology Network were breast cancer (45%), colorectal carcinoma (14%) and lung cancer (7%). For men they were colorectal carcinoma (24%), lung cancer (22%) and prostate cancer (10%). See diagram 1.

Cancer stages at first diagnosis and start of documentation in the Oncology Network were comparable to those of other registers. The ratio of conventional therapies in the Oncology Network was 92%. 80% of all patients received mistletoe applications, and 63% received non-pharmacological therapies (e.g. psycho-oncological care, artistic therapies, external applications and eurythmy therapy).

The findings show that mistletoe therapy is the most used complementary therapy in the Oncology Network. It is used to strengthen self-regulation, to reduce chemotherapy-induced side effects and to improve quality of life in the oncology realm. Complementary anthroposophic (so-called multimodal, non-pharmacological) therapies, used for over half of the Oncology Network patients, help the patient to activate his own resources and improve his overall state of wellbeing.

One important theme is the safety of using mistletoe, and any associated side effects, primarily related to interactions with other medicines. With the help of the side effects profiles recorded in the Oncology Network, we were able to show that both the standard subcutaneous and intravenous injections of mistletoe (the latter often in combination with intravenous chemotherapy) are safe for patients and are associated with only a few, mild to moderate (intravenous 4.6%, subcutaneous 8.4%) side effects, some of which are known and intended (inflammation at the injection site and raised temperature/fever). Overall, mistletoe therapy is therefore safe to use [2, 3].

Analyses of interaction with other medicines showed that the side effect rate in oncology patients treated with monoclonal antibodies and additionally with mistletoe is five times less than in patients who receive monoclonal antibodies without adjuvant mistletoe therapy. [4] (see also table 1).

In the last five years new types of therapies, known as immune-oncological therapies (such as Nivolumab, Ipilimumab and Pembrolizumab), have been registered in accelerated procedures by American and European supervisory authorities since they can markedly improve survival rates in patients with advanced or metastized melanomas and lung cancer. Previously there were no safety findings for use of these promising therapies with adjuvant mistletoe therapy. Because of this we studied a small cohort of 16 patients with either advanced or metastized melanoma or lung cancer, and were able to demonstrate that adjuvant administration of mistletoe did not lead to an increase in side effects [5]. It should be noted here that Nivolumab and the other named new types of immune-oncological medicines are associated already with a high

Monoclonal antibodies	Combined Therapy		mAB Therapy	
	Exposures	Exposures with ≥1 AE (%)	Exposures	Exposures with ≥1 AE (%)
Ado-trastuzumab emtansine	17	1 (5.8)	-	-
Bevacizumab	188	32 (17.0)	18	9 (50.0)
Cetuximab	146	20 (13.7)	4	2 (50.0)
Ofatumumab	-	-	3	2 (66.7)
Panitumumab	12	1 (8.3)	1	1 (100.0)
Rituximab	4	0	6	1 (16.7)
Trastuzumab	107	7 (6.5)	36	3 (8.3)

Table 1. Incidence of side effects after therapy with monoclonal antibodies with and without mistletoe. Combined therapy = monoclonal antibodies and mistletoe therapy, bAb = monoclonal antibodies, Exposures = treatment. Source: reference 4

rate of side effects, especially immunologically-related ones such as bronchitis, colitis (acute or chronic inflammations of the large intestine) or skin rashes. When treated, these usually fade.

In recent years, understanding of the quality of life of individual patients – a core area of anthroposophic medicine – has increasingly been foregrounded by modern oncology. This primarily involves evaluation of internationally validated questionnaires, which reproduce what patients state about their sense of health and wellbeing in symptomatic (e.g. pain, bloatedness, nausea, fatigue) and functional (emotional, social) areas, as well as in their personal experiences of life quality.

In evaluating these questionnaires completed by 99 breast cancer patients in the Oncology Network, who either received mistletoe in addition to guideline-correct standard therapies, or only the standard therapy, we found the following. For breast cancer patients receiving adjuvant mistletoe therapy, a significant improvement was achieved in emotional and social functions six months after first diagnosis – that is, patients were less tense, less worried, less irritable, or felt less downcast (emotional function). Likewise their physical condition, or the medical treatment received, was less of an impairment to family life and interaction with others (social function). The patients also found that they were less restricted in their work, their daily life and leisure time (role function) compared to the point six months earlier when they received their first diagnosis. By contrast, patients who did not receive adjuvant mistletoe therapy alongside conventional therapy did not show these improvements after six months. The findings of this health services research study were presented at the interdisciplinary Quality of Cancer Care congress of the German Cancer Association in 2017, and the World Congress of Integrative Medicine & Health 2017 [6, 7].

To sum up: anthroposophic integrative oncology is drawing large numbers of patients who seek clinics and practices with an anthroposophic orientation. Despite its widespread use, integrative oncology needs to be studied further in clinical practice. The Oncology Network register offers an infrastructure for studying integrative concepts, comparing them with other clinical registers and thus contributing to improved provision in this field. Given the extremely high costs of the newer oncological medicines especially, we also aim in future to draw on Oncology Network data to analyse the cost effectiveness of mistletoe therapy in the integrative anthroposophic context. ■

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Mistletoe research – from the laboratory to the patient

DR. ULRIKE WEISSENSTEIN

For many years we have investigated the efficacy of Iscador both with the help of laboratory experiments and clinical studies. It was discovered in the 1980s that mistletoe extract has a toxic effect on cancer cells. At the same time the treatment with mistletoe appears to have a protective function for healthy blood cells. After chemotherapy or radiotherapy supported by mistletoe therapy, a clear deterioration in certain blood values occurs less frequently.

A lot of research work has been devoted to the action of mistletoe extracts such as Iscador on the immune system. The processes in the body's own defences are very complex. Cancer cells develop characteristics and strategies by which they can evade the immune response. Today it is deemed to have been proved that the immune system can recognize and eliminate cancer cells. This presumably happens very frequently in healthy people and it is assumed that when cancer occurs the body's immune system is in certain respects too weak or not in a position to recognize the cancer cells as foreign and dangerous to the body.

Cancer itself, like the treatment with chemotherapy or radiotherapy, often leads to a reduced number of white blood cells which can lead to a weakening of immune function. One goal of treatment with Iscador is to strengthen the body's natural defences. Treatment with Iscador stimulates both the natural immune system and specific immune resistance. Iscador acts to support the maturation and activity of different types of immune cell (e.g. natural killer cells, macrophages, dendritic cells or T lymphocytes). The liposoluble component of mistletoe shows an effect that supports wound healing. Here, too, there are indications that immunological effects are co-responsible for this action.

The focus of our research work in recent years included investigation of the interaction between Iscador and standard oncology drugs. The interaction between different medicines might potentially change their action. Hence it is necessary to know about potential medicinal interactions. We tested the influence of various chemotherapeutic substances on cancer cells in the test tube but also the action of Iscador on Herceptin and Tamoxifen. Our laboratory experiments showed no cases where the efficacy of the cancer drugs studied was reduced by Iscador. These results provide a foundation for the parallel use of Iscador and conventional treatment, an approach which has proven successful in practice, particularly with regard to quality of life. Iscador and conventional treatments appear to work on different levels, which explains their good compatibility.

We will continue our research in this direction. In the next few years patients will be treated with many new modern drugs, so-called targeted therapies. Some of these therapies aim to stimulate defence against tumours in the immune system of cancer patients, which has frequently been suppressed. In our view Iscador could be an excellent combination partner here. One of the ongoing research projects is concentrating on this question.

Various clinical studies have shown that the patients treated with mistletoe benefited a great deal in terms of improvement in their quality of life. One factor which can have a very detrimental effect on quality of life is so-called cancer-related fatigue. It is a state of pronounced weakness, exhaustion and lack of drive which does not improve with sleep or rest. In our projects we are investigating the special effect of Iscador on this symptom of cancer, both experimentally and in clinical studies. Here the focus of laboratory research is on explaining the mechanism of the action of Iscador in improving fatigue, something required for a broader acceptance of mistletoe therapy. In accordance with our current hypotheses the energy balance as well as the rhythms of body temperature or the body's own hormones could play an important role.

In our future research work we will increasingly concentrate on complex physiological processes and connections. How does mistletoe therapy influence the interaction of immune system, nervous and hormonal system? What role is played by metabolism and rhythm? How can they be positively affected to benefit patients?

Skills in various specialist areas are indispensable for our scientific projects. Hence we are collaborating closely with physicians and researchers at home and abroad to achieve our goals. ■

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Mistletoe extracts neutralize tumour-induced immune suppression in a human cell culture model

PD DR. CARSTEN GRÜNDEMANN

Tumour cells occur naturally in the human organism but as a rule these cells are recognized and eliminated by the immune system. Here the interaction of antigen-presenting cells such as the dendritic cells, as they are known, and related immune cells, the natural killer cells (NK cells) and T-lymphocytes plays an important role [1, 2]. Tumour cells however have the ability to secrete immune-suppressive substances such as vascular endothelial growth factor, prostaglandin E2 and various cytokines [3-6] and thus to create an immunosuppressive environment which allows the tumour cells to conceal themselves from the immune response. Activated dendritic cells are the strongest antigen-presenting cells of the human immune system [7] and are crucial for stimulating the specific immune response. They are in a position to eliminate tumour cells in the body [8-10].

The action of mistletoe extracts (Viscum album) on the process of tumour-mediating immunosuppression in the cell culture described above has already been studied in a previous project. The results of the past project show that Iscador can both stimulate the maturation of dendritic cells and counter the tumour-mediating inhibition of dendritic cell maturation.

The question as to the role played in this process by mistletoe lectin was investigated in a current research project. Using the already established cellular system, the influence of Iscador on the maturation of human dendritic cells and on T-cell function was examined. Another subject of investigation was whether Iscador is capable of countering tumour-induced immune suppression. The role of mistletoe lectin was analysed using mistletoe lectin-specific antibodies and mistletoe lectin-depleted Iscador.

Iscador strengthened the maturation of dendritic cells. Co-cultivation experiments of dendritic cells and purified CD4+-T-cells

did not show that T-cell proliferation or interferon gamma secretion by T-cells was affected by Iscador. Iscador was also able in the current experiments to counter the tumour-mediating inhibition of dendritic cell maturation. Both stimulation of dendritic cell maturation and prevention of maturation inhibition by tumour cells was facilitated by mistletoe lectin since mistletoe lectin-specific antibodies and mistletoe lectin-depleted Iscador virtually neutralize the rehabilitative effect of Iscador.

Due to the prominent role of dendritic cells in the defence against tumours, the study suggests a possible new mode of action of Iscador as an additive cancer therapy on the basis of immunomodulatory effects. The effect on humans will, however, have to be evaluated in further studies. ■

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Mistletoe and other oncology therapies

ALEXANDRA LEMCHE

Background

Cancer is a very complex disease. A tumour may not necessarily contain just a single molecular biological form of cancer but several different cancers can exist alongside one another. In breast cancer there are, for example, seven different subtypes which can also occur in parallel. Each one of them then requires different treatment. A complex disease requires complex treatment. Progress in treatment means that the typical course of cancerous diseases will increasingly come to resemble a chronic disease. Increasing numbers of people who would previously have died of cancer will survive, even if the cancer cannot be completely cured in all cases. As a result of the anticipated increase in such «chronic courses of cancer», continuous follow-up treatment and careful long-term oncology care will grow in importance. One paradigm change in the battle against cancer now consists of the situation that in view of the complexity of the disease the goal of cancer treatment is no longer primarily to «heal» but shifts to «stabilizing and living with cancer».

Mistletoe therapy has for many decades been among the most frequently used and studied forms of complementary tumour treatment in Germany. Mistletoe extracts are used both to support other cancer therapies, and in the treatment phase; and also for follow-up care. It is, however, the case that so far there has not been sufficient reporting about

the interaction of mistletoe therapy with other anti-tumour cancer treatments. The interaction between medicines can lead to desired, deliberately used effects, but also to reduced and undesirable ones.

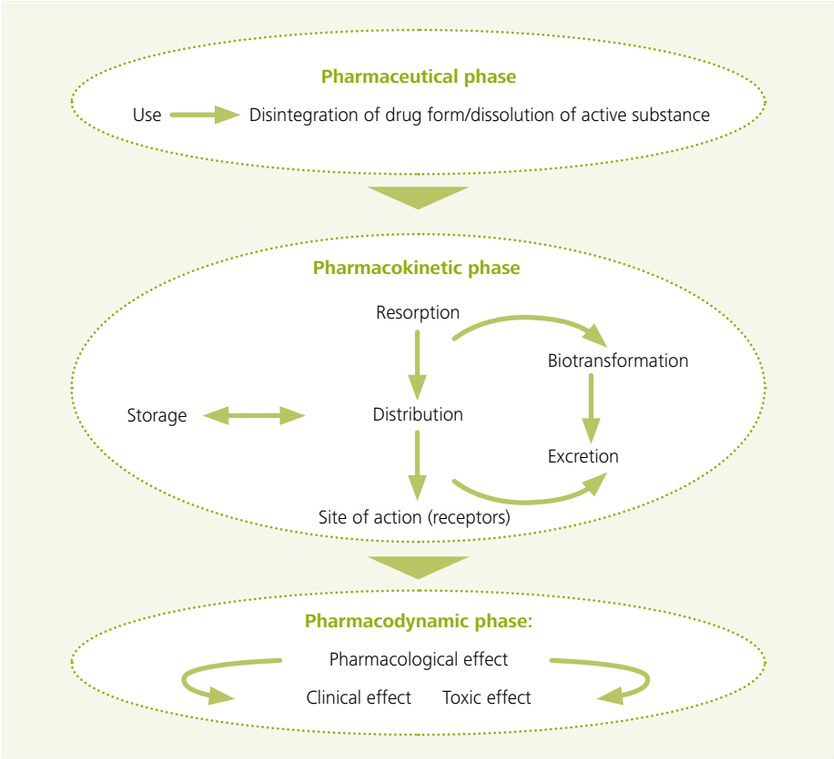
The aim of this article is to provide an overview of existing research results in this field and to uncover gaps in knowledge so that the direction of further research can be defined.

Drug interactions

Drug interactions are changes in the pharmacodynamics and/or pharmacokinetics of a pharmaceutical substance produced through the simultaneous administration of another pharmaceutical substance, foodstuffs, smoking and/or alcohol.

A differentiation is made between **pharmacodynamic** and **pharmacokinetic** interactions.

Pharmacodynamic interactions mean the reciprocal effects in which pharmaceuticals directly influence one another. As a rule sedative drugs for example can reinforce one another. That also applies to alcohol which can increase the sedative effect of many different drugs in a nonspecific way. Often, however, a pharmacodynamic interaction is wanted if aligned, reciprocally reinforcing (synergistic) effects are achieved as a result, for example in the use of anti-infective agents or in pain therapy. If the effect of a medicine is obstructed by another, it is called an antagonistic effect. Examples of pharmacodynamic interactions are the simultaneous administration of NSAIDs and Phenprocoumon (additive interaction) as well as ASS and Ibuprofen (antagonistic interaction).



Basics of drug interactions

Pharmacokinetic interactions include those at the levels of assimilation (example: Levothyroxine and neutralising antacids), excretion (example: Digoxin and macrolides) and metabolism, as in the competition for cytochrome P450 enzymes (example: SSRI and certain beta-blockers).

Mistletoe and oncology treatments

Numerous clinical studies have shown the effects of the interaction between mistletoe and other oncology treatments (chemotherapy, radiotherapy, hormone therapies, etc.) on the course of cancer and the quality of life of cancer patients.

These studies mostly investigated the interaction in the pharmacodynamic phase, and in particular the effect on treatment effectiveness and on the alleviation of unwanted side effects (safety) of anticancer therapies.

The mechanisms of mistletoe action include:

- Cytotoxic effect on the cancer cells (apoptosis)
- DNA-stabilizing effect (protection of healthy tissue)
- Immune-modulating effect (improvement of the body's own regulatory processes)

The main objectives of combining chemotherapy, radiotherapy and other biological therapies with mistletoe therapy are:

- Reinforcing control over the disease (prolonging disease-free period and overall survival, initiation of remission)
- Improvement in the tolerance of treatment for the patient through alleviation of side effects
- Reduction in the fatigue and exhaustion caused by cancer and cancer therapies
- Improvement in the patient's quality of life

The most convincing and consistent results come from quality of life studies which investigated the effects of mistletoe therapy supporting conventional therapies:

- improved tolerance of regular tumour therapies (by reducing unwanted toxic effects)
- improvement in quality of life (particularly quality of life affected by side effects)

Some results in the studies on the reinforcement of the clinical effect of regular tumour therapies (additive or synergetic interaction) are the subject of controversial debate. Scientists attempted to clarify in a whole range of studies whether patients suffering from cancer benefited from mistletoe therapy in that it prevented a relapse (prolongation of disease-free survival), promoted remission or brought about an overall survival benefit. A summary analysis of the effect of Iscador treatment on survival time reached the conclusion that Iscador treatment in addition to standard therapy approximately doubles the anticipated survival time.

Interactions of the pharmacokinetic phase

The data in the few studies concerned with questions relating to metabolism-based interaction between mistletoe and other drugs have so far been inadequate and contradictory.

Summary:

1) The interactions between a mistletoe extract and other oncology therapies trigger usable synergetic effects which maximize the clinical activity of these therapies and lead to greater benefits for cancer patients.
2) Adverse effects from mistletoe with regard to the action of other oncology therapies (antagonistic effects) have not so far been found.
3) Further clinical and preclinical studies are required to identify potential synergetic effects and their biological mechanisms in the adjuvant use of mistletoe therapy in addition to standard oncology therapies. ■

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Mistletoe therapy for cancer-related fatigue and insomnia

PD DR. MATTHIAS KRÖZ, DANILO PRANGA

In recent years, scientific interest has increasingly focused on the importance of cancer-related fatigue and insomnia (sleeplessness) as symptoms of cancer patients.

Even years after oncology treatment has ended, breast cancer patients continue to suffer from this fatigue even if the cancer does not return. Three years after surgery, chemo- or radiotherapy, 35-40% of breast cancer patients continue to show cancer-related fatigue, and after ten years the figure still remains at 17 to 34%.

Alongside fatigue, sleep disturbances are also very common long-term symptoms, especially in breast cancer patients. One study found insomnia in 51% of patients four years after initial diagnosis, and in 19% of them this fulfilled the criteria for a pronounced condition lasting over a month, known in medical terminology as «insomnia syndrome».

The best therapies currently available for treating cancer-related fatigue are non-medicinal procedures, especially endurance training (guided by a trainer) and cognitive behaviour therapy approaches such as sleep clinic counselling and recommendations for bedtimes and bedtime restrictions. Medicinal treatments (except for transfusions in the case of severe anaemia) such as stimulants are contentious and even, as in the case of Erythropoetin, associated with an increase in mortality rates. Now, with increasing awareness that the use of mistletoe extracts parallel with chemotherapy may reduce the undesired side effects of the latter and thus improve the quality of a patient's life, mistletoe therapy is also in the spotlight in relation to cancer-associated fatigue.

A literature search in databases of scientific journals up to and including 5 January 2015 produced 13 articles on the connection between mistletoe use

and cancer-related fatigue or exhaustion. Ten (randomized, controlled) studies were included in one systematic review.

The studies were on patients with the following cancer types: breast cancer (four studies) non-small-cell lung carcinoma, pancreatic carcinoma, bone tumour (osteosarcoma), stomach carcinoma and head-and-throat carcinoma (one study on each), as well as a further study covering three different cancer types: breast cancer, non-small-cell lung carcinoma and fallopian cancer.

All the studies recorded patient quality of life. Seven of these studies did so using the questionnaire of the European Organization for Research and Treatment of cancer (Quality of Life Core Questionnaire, or «EORT QLQ-C30»), two used the Global Quality of Life («GLQ»), one the Functional Assessment of Cancer Therapy – General («Fact-G») and a last used the Traditional Chinese Medicine Scale («TCM Scale»). These questionnaires record fatigue or sleep disturbance in different ways.

In six out of ten studies, mistletoe therapy significantly reduced cancer-related fatigue or tiredness, and in six out of nine studies also insomnia (three of these studies concerned breast cancer, and one each related to osteosarcoma, pancreatic cancer patients and patients with several cancer types).

In all these questionnaires, however, there were at most three questions relating to cancer-related fatigue. This is insufficient to adequately record the complex symptomatology of cancer-related fatigue and insomnia. Thus the questions offer an indication but as yet no full evidence of the efficacy of mistletoe therapy for treating cancer-related fatigue, especially since no mistletoe therapy studies have yet been conducted with the parameter of cancer-related fatigue as their prime focus. Current questionnaires containing 10 to 20 questions on cancer-related fatigue are, for instance, the Multidimensional Fatigue Inventory («MFI») with a total of 20 questions, the Cancer Fatigue Scale («CFS») with a total of 15 questions or, in relation to sleep quality, the Pittsburgh Sleep Quality Index («PSQI») with 18 questions.

Nevertheless, researchers believe there are already adequate indications that mistletoe therapy can help to reduce or ameliorate symptoms of fatigue and insomnia in cancer patients receiving chemotherapy or undergoing other adjuvant treatment procedures.

Descriptions now exist for a wealth of findings on the use of mistletoe therapy: these include effects at the level of single immune-cell types, cancer-cell-death-promoting (pro-apoptotic) actions, cancer blood supply-inhibiting (anti-angiogenetic) and immune-stimulating actions.

At present it remains an open question whether and how mistletoe therapy acts upon chronic inflammation or possibly affects the pattern of sleep in the context of cancer-related fatigue. These questions will require future clarification through fundamental research and further clinical trials.

In conclusion, symptoms of fatigue or tiredness were shown to improve in 60% of modern studies, while symptoms of insomnia improved in 67% of the studies, even though the questionnaires used were not adequate to encompass all details of these complex disorders. In future, therefore, questionnaires should be chosen and used with specific regard to these symptoms in studies on mistletoe treatment primarily focusing on fatigue and insomnia.

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The glue-like substance of mistletoe – research emphasis of the Hiscia Research Institute

DR. KONRAD URECH, DEVIKA SHAH, PETRA ZIBULSKI, DR. JAKOB MAIER

A glue-like substance has been extracted from mistletoe since antiquity. It was used as birdlime into the modern age. A reference by Rudolf Steiner about the importance of this glue substance with regard to the antitumoral action of mistletoe preparations [1] led to it becoming a research topic at the Hiscia Institute (Society for Cancer Research). Cross-departmental projects revealed the key position of this substance in botany, pharmacology, pharmaceutical processing and the clinical use of mistletoe.

As long ago as 1833 the glue-like substance in mistletoe became the subject of academic research and was given the name «viscin» [2]. This is a resin-like, purely liposoluble substance which occurs in all the green organs and berries of mistletoe. In its isolated form it displays its extraordinary stickiness and rubber-like elasticity. The droplets of viscin embedded in the mucilaginous pulp of the berries give the mistletoe berries their white colour (Fig. 1) and in our experiments turned out to play a vital role in the survival of mistletoe. They are responsible for the mistletoe seeds adhering to the bark of the host tree (Fig. 2).

We were able to show that viscin inhibits the growth of cultivated tumour cells because it triggers so-called «programmed cell death» (apoptosis). In searching for the principle which triggers apoptosis, we identified seven different triterpene compounds and at least two phytosterols as components of viscin [3]. The literature describes a spectrum of the greatest variety of interesting pharmacological effects of these compounds: they include antitumoral, antiviral, antiulcerative as well as analgesic effects. Our own preclinical studies were able to show stimulation of wound healing [4] and immunologically relevant effects in leucocytes from subjects' blood [5]. Antitumoral, wound heal-

Fig. 1: Ripe mistletoe berries.
Photo: J. Buess

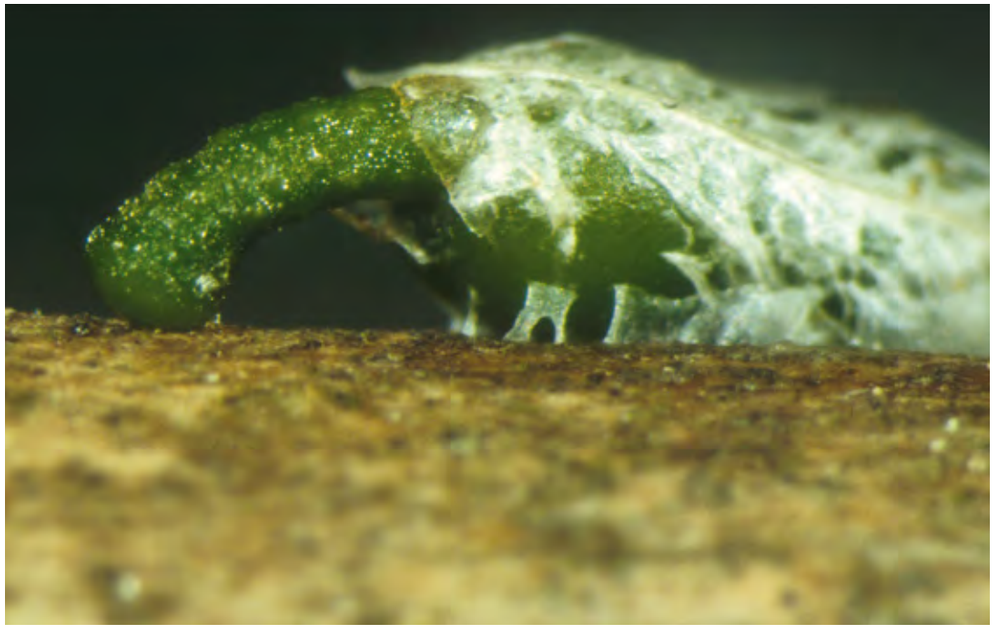

Fig. 2: Germinating mistletoe seeds with their lime substance glued to the bark of the host tree.
Photo: H. Ramm

ing and immunomodulating effects are three fields which are closely interconnected. Thus we are trying to develop a better understanding of the pharmacological efficacy of viscin.

We aim to take the multiple pharmacological effects which have been found in viscin into account in the pharmaceutical development of viscin-containing preparations. To this end the extraction of this liposoluble «active substance» was first evaluated, whereby «supercritical CO_2» turned out to be the optimum extraction medium. The extract thus obtained in the composition typical of mistletoe now forms the basis for processing it further into a remedy.

Our current development of preparations goes in two directions. The first project covers work to produce an injectable aqueous emulsion of lipophilic viscin. The pharmaceutical task is to turn this mistletoe substance into the form of an emulsion. The viscin droplets have to be reduced to a size at which they remain stable and can pass through the small mesh of a sterile filter. This will for the first time provide the opportunity to use not just the water-soluble substance of mistletoe as hitherto, but to incorporate the action of the «whole» mistletoe by admixture with its hydrophobic part. This ambitious project is well underway and, as the focus of the research and development work, will draw on a considerable part of the energy and resources of the Hiscia Institute.

In another project – taking into account the pharmacological effects of viscin that we demonstrated – we set about producing a topically applicable ointment [6]. Observational studies with this ointment (Viscum album, Resina 10%, Unguentum – extemporaneous preparation) are already showing positive results for various indications including actinic keratosis, basal cell carcinoma and cutaneous squamous cell carcinoma [7]. Using this preparation we succeeded, for the first time, to demonstrate that this mistletoe substance – still full of secrets – recommended by Rudolf Steiner for use in cancer treatment, has an anti-tumour action.

We are confident that the development of viscin-based preparations can substantially enhance the therapeutic options in cancer treatment for the benefit of patients. ■

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Experiences from the Klinik Arlesheim

Interview with Bettina Böhringer

INTERVIEW BY RAHEL WITTWER

We can look back now on a century of mistletoe cancer therapy. Today's Klinik Arlesheim is intrinsic to this history. Can you tell us something about the clinic's origins and development?

It all goes back to the founder, Ita Wegman. She attended a lecture by Rudolf Steiner where he said that his spiritual-scientific findings should flow into actual practice and thus be tried and tested in a clinical context. For Ita Wegman these words were decisive for founding a clinic where Rudolf Steiner's impulses and insights could be introduced, applied and further developed. After discussions with other physicians, who offered her the necessary support, she bought the Hirsland estate in Arlesheim and opened the clinic on 8 June 1921. Rudolf Steiner was the first to visit it, and spontaneously said that he looked forward to working with her, and would like to call the clinic the «Clinical-Therapeutic Institute». In the following three-and-a-half years, she and Steiner engaged in lively dialogue, and whenever he was staying near by he visited the institute every day to discuss patients, look at case histories and conceive therapies, thus initiating anthroposophically extended medicine. One of the chief remedies used from the beginning was the mistletoe preparation developed by Ita Wegman and the pharmacist Hauser, which in those days was called «Iscar».

Personal details:

Bettina Böhringer is senior physician in the oncology department at Klinik Arlesheim AG.

In 1935 Ita Wegman founded the Society for Cancer Research in collaboration with Rudolf Hauschka, and Lina and Werner Kaelin. How was the Society connected with the clinic?

The life and impulse of Alexandre Leroi played a key role here. He arrived at the institute as a physician in 1934, having felt strongly drawn to Ita Wegman, and feeling a deep wish to work with her.

Sadly their collaboration was short-lived since Ita Wegman left the clinic only a little while later. From the beginning Alexandre Leroi was an incredibly strong proponent of mistletoe research and therapy, and the moment he arrived he also joined the Society for Cancer Research. He was very committed both to the Society and the clinic. He had a special gift for relating to patients, which meant that patients even travelled from abroad to Arlesheim to be treated by him. His great wish was to open an oncology department at the Clinical-Therapeutic Institute. This did not happen however, and so he kept discussing the idea at the Society for Cancer Research. Disunity about this led to a kind of division and separation process resulting in some of the clinic's physicians leaving the Society for Cancer Research when they saw the conflict intensifying. By contrast, Alexandre Leroi himself worked with increasing commitment within the Society, and pursued his desire to found an independent clinic for treating cancer and developing the mistletoe preparation. Thus the overriding impulse of his life came to fruition: development of a tripartite project consisting of research (mistletoe and cancer research), clinic (practical application) and training (medical training centre). This was an incredible vision, with incredible dynamism. As a first step towards realization, the Lukas Klinik was founded in 1963 under the direction of Rita Leroi, the wife of Alexandre Leroi and one of the great, legendary anthroposophic physicians. Alexandre Leroi himself never took over management of the clinic but withdrew from it to focus more strongly on research. The Lukas Klinik became the centre for anthroposophic cancer therapy, and remained so for a long time. When Alexandre Leroi died five years later, Rita Leroi carried on his impulse. Under her leadership the Lukas Klinik gained a worldwide reputation for treating cancer patients, and she was also the president of the Society for Cancer Research. When, in addition, she founded the doctors' seminar with Friedrich Lorenz, she fulfilled her deceased husband's vision. It was Rita Leroi's huge achievement to bring anthroposophic cancer therapy into clinical practice, and to communicate this to physicians throughout the world by travelling a great deal and giving lectures. Thus she enabled patients in Europe primarily, but also worldwide, to receive anthroposophic cancer treatment.

Now the Clinical-Therapeutic Institute (since 1971 the Ita Wegman Klinik) and the Lukas Klinik, where you worked for many years, have joined forces to become Klinik Arlesheim. In your view, what effect have these changes had, and what does this mean for patients?

Over the past 50 years at the Lukas Klinik, an oncology practice characterized by complete dedication to patients developed. This involved close collaboration between nurses, artistic therapists, eurythmy therapists, biographical counsellors and physicians, together with application of the mistletoe preparation Iscador, as developed by the Society for Cancer Research. At the Ita Wegman Klinik, too, a small core of physicians concerned themselves with anthroposophic oncology. The emphasis there lay on the diversity of available mistletoe preparations and in the supplementary use of hyperthermia treatment. The knowledge and experience of both clinics can now be amalgamated to enrich patient provision. Patients are introduced into our community of physicians, observed, perceived and discussed, and this leads to the best possible treatment for each individual, offering a therapeutic diversity that did not previously exist in the same way, and is almost unique in this clinic. Patients benefit from the knowledge of all the physicians here, not only from that of a single one. Additionally, drawing on the resource of different mistletoe preparations, a new diversity arises, and the chance to acquaint ourselves more deeply with, and make more differentiated use of, each preparation and also its various modes of application (subcutaneous, intratumoral, intravenous).

How do you view the place of complementary cancer therapy in modern oncology?

Complementary medicine is currently in vogue. Many of the patients diagnosed with cancer seek a complementary medical approach. There is an impressive diversity of complementary medical approaches, but this can often be confusing for patients. How can they find the right one for them? Our oncology provision is distinguished by our holistic view and treatment of patients, and our capacity to offer them the best possible combination of mainstream oncology and complementary therapies such as mistletoe. From August 2017 we will gain the strong support of Dr Marion Debus, currently an oncologist in Berlin. We are likewise developing close collaboration with an oncology department in the vicinity, and thus increasingly working towards integrating developments in conventional oncology.

As senior physician in the oncology department here, you have been using mistletoe therapy for many years in combination with other cancer treatments. What do you think is the special value of mistletoe therapy?

Mistletoe extracts certainly demonstrate cytotoxic and also immune-modulating actions. At the dynamic level, patients receiving mistletoe treatment feel more lively, capable, and better in general. Their whole neuro-vegetative anamnesis improves, including their appetite, sleep and levels of tiredness. At the emotional level, after medium-term treatment, it becomes apparent that patients are more content with themselves and their surroundings. Anxiety diminishes and slight melancholy or possibly depressive tendencies improve. Longer-term treatment has shown, worldwide, that patients develop

a new sense of purpose and find meaning in their illness. The sense of freedom they develop in relation to their illness is very striking: they shape their own lives and do not allow the illness to dominate everything.

How would you like to see anthroposophic oncology developing in future?

I may not be the right person to judge this. I concern myself with patients – this is my be-all and end-all. But my experience tells me that treatment nowadays is expected to be «evidence-based», thus founded on empirical proofs. Especially when I give talks or take part in oncology conferences, this repeatedly strikes me. Everything nowadays has to be «evidence-based». Even patients who come here do so sometimes because of a certain kind of evidence-based information. For instance, their neighbour might say they are taking mistletoe and it has been helping them – a type of small, uncritical «evidence». My very personal and humble view, therefore, is that we must accustom ourselves to produce evidence supporting our approach in the public domain if we wish also to persuade a critical audience. There are some good scientific studies, especially on mistletoe therapy. I am not yet entirely clear where our future task lies. Will it be in helping researchers and physicians to work more closely together, so that one knows exactly what data are available? Or will we need to undertake still more research, even of a simple kind, in order simply to make it publicly known? If anthroposophic medicine is to survive, and be taken seriously in the mainstream medical world, it will probably need a combination of all these things. I am glad that a bridge remains between oncology at Klinik Arlesheim and the Society for Cancer Research. And yet this bridge ought to become a great deal broader and stronger. We have data collected from 50 years of practice at the Lukas Klinik; and building on this we want to work together for the future of anthroposophic oncology. To survive in future we will need still more trials and studies. ■

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