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# Biotherapy - History, Principles and Practice

## A Practical Guide to the Diagnosis and Treatment of Disease using Living Organisms

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# Preface

Biotherapy – the use of living organisms for the treatment of human and animal illness – is a practice known since antiquity. But it is not antiquated! Thanks to modern scientific methods and the dedication of many clinicians, biologists, biochemists, and patient advocates, biotherapy today is a rapidly advancing multi – disciplinary field of medicine. The story of biotherapy is a story of life and evolution, a story of human history, a story of scientific discovery, a story of deadly diseases and miraculous cures. The story of biotherapy, as revealed in these pages, is the story of life itself, and the story of man's will and capacity to harness the power of life. The story of biotherapy teaches us that all living beings on this planet are interrelated. Occasionally, those relationships can be beneficial to both parties. Biotherapists have found or created such mutually beneficial relationships, in their efforts to tackle illness and disability. This is their story, too.

The body of scientific publications concerning biotherapy has grown astonishingly large, especially during the past several decades. Much of the credit for biotherapeutic discoveries must go to open-minded and observant clinicians and scientists. The observations of biotherapists provide strong evidence of the concept and power of evolution. It is reasonable to expect that two organisms living together, one parasitic on the other, would eventually (if given enough time) alter their biology or behaviors in such a way that they could both thrive together. After all, if the host cannot survive invasion by the parasite, its species will eventually come to an end. And if the parasite kills its host, then another host must be found (a major waste of time and energy). It is mutually beneficial when both organisms can coexist. Evolution is not simply about "survival of the fittest." It is about adapting to one's condition, so as to become more fit. Biotherapists have recognized many such adaptations that evolved around problems of illness. They have also adapted other inter-species relationships in order to apply them to unmet health needs. This treatise is filled with examples of both.

Take, for example, the blow fly maggot, which evolved to live in the most hostile environments: decaying carcasses, teeming with highly pathogenic bacteria. Clinician researchers, observing that blow fly larvae can also infest wounds in live hosts – and remove the dead tissue from those wounds, without harming the live tissue – began intentionally applying maggots to the non-healing wounds of their patients.

Today, maggot therapy is one of the most rapidly advancing fields within biotherapy, having already gained acceptance by the medical establishment and by health care regulatory authorities.

Need often drives innovation. Better treatments for infectious diseases remain a powerful need these days, because so many of our antibiotics are now useless against the microbes which developed resistance to them (another example of adaptation). This need for better defense against infection is helping to open doors for maggot therapy and other biotherapeutic modalities (e.g., phage therapy). Corpse-dwelling maggots coevolved with bacteria, and now their antimicrobials are proving to be effective in hospitals against the microbes, which have become resistant to man's antibiotics.

Maggot therapy epitomizes some of the common benefits of biotherapy: effective, relatively safe, and low-cost treatment of serious medical problems (in this case, diabetic foot ulcers, pressure ulcers, and other problematic or recalcitrant wounds). When performed responsibly, biotherapeutic modalities have little or no impact on the environment and can often be administered by paramedical personnel rather than highly trained medical specialists.

Hirudotherapy – the medical use of leeches – is one of the oldest practices in all of medicine. Over the years, hirudotherapy has evolved from a simple bloodletting procedure to a scientifically based physiologic process with rationally defined clinical applications. During the Middle Ages, the golden era for bloodletting, leeches were used by nearly every physician to cure anything from headaches to hemorrhoids. In Russia, hirudotherapy reached its zenith in the late eighteenth and early nineteenth centuries, when leech harvesting and leech therapy netted the country an annual six million silver rubles. By the end of the nineteenth century, leeching fell out of favor and became associated with medical quackery in most countries. However, the past 25 years have seen a renaissance in leech therapy, primarily because of its newfound value in reconstructive, transplant, and microvascular surgery. Nowadays, leech therapy is a standard treatment for postoperative venous congestion and has become an integral part of the armamentarium to salvage vascularly compromised flaps or replants. In the twenty-first century, several clinical studies were performed in Germany and Russia demonstrating the efficacy of leeches in relieving osteoarthritis pain. In Asia, Russia, and parts of Eastern Europe, hirudotherapy is officially recognized as a classic alternative treatment for diseases such as phlebitis, osteoarthritis, hypertension, and glaucoma.

Therapy with honey bee venom (HBV) is a bio-therapeutic treatment that utilizes the venom of honeybees. Physicians dating back to Hippocrates used HBV to treat a variety of illnesses. Today, physicians are using bee venom to treat patients with chronic pain disorders such as rheumatism and arthritis, and to combat many inflammatory and degenerative connective tissue diseases. Neurological disorders such as migraines, peripheral neuritis, and chronic back pain are also being treated successfully with HBV. In the case of autoimmune disorders such as multiple sclerosis and lupus, bee venom restores movement and mobility by strengthening the body's

natural defensive mechanism. In addition, dermatological conditions such as eczema and psoriasis, and some infectious diseases such as herpes and some urinary tract infections, have been effectively treated.

Apitherapy is the science and art of the use of honeybee products to regain and maintain health. In the past, products of the hive, that is, honey, pollen, propolis, and royal jelly, were frequently used as natural remedies for health maintenance, while bee venom was used for the treatment of illness. More recently, the products of the hive have been incorporated into Western medical practice, where the focus of attention is mainly on illness and its prevention.

Helminth therapy – the therapeutic introduction of helminths (parasitic worms) into the body – provides another example of host-parasite evolution. Over the course of millions of years, helminths and their human hosts have developed mechanisms to co-exist relatively well. In order to survive our immune system, many parasitic worms developed mechanisms to modulate (alter) their hosts' normal immune defense mechanisms. At the same time, mammals optimized their immune responses so as to prevent excessive and potentially lethal invasion by helminths. There are more than 80 different autoimmune diseases, which afflict people in highly developed industrialized countries, but they are rarely seen in tropical countries, where helminth exposure is common. As countries eradicated helminth infections over the past century, autoimmune and inflammatory diseases rose significantly. With exposure to helminths again, many patients with autoimmune and inflammatory diseases have experienced significant remission of their symptoms. Two such helminths – the porcine whipworm, *Trichuris suis*, and the hookworm, *Necator americanus* – were recently evaluated for potential medical application, with very encouraging results. Diseases currently being studied for treatment by helminths include Crohn's disease, ulcerative colitis, multiple sclerosis, celiac disease, rheumatoid arthritis, and autism. Furthermore, such observations and experiments have provided new insights into the complex interactions between helminths and their hosts. With these insights has come a better understanding, and novel treatments, for several autoimmune and inflammatory diseases.

Ichthyotherapy is defined as the treatment of skin diseases such as psoriasis and ichthyosis with the so-called doctor fish of Kangal, *Garra rufa.* Pilot clinical studies and numerous anecdotal reports indicate that ichthyotherapy is a promising treatment for these conditions and deserves further study.

Phage therapy is the use of bacteriophages – viruses that can only infect bacteria – to treat bacterial infections. In some parts of the world, phages have been used therapeutically since the 1930s. Phage therapy was first developed at the Pasteur Institute in Paris early in the twentieth century and soon spread through Europe, the USA, the Soviet Union, and other parts of the world, albeit with mixed success. With the advent of chemical antibiotics in the 1940s, phage therapy found itself largely ignored in the West, though it continued to be used to varying degrees in some other countries, with claims of success. Today, however, the resurgence of bacteria that are resistant to most or all available antibiotics is precipitating a major

health crisis, and interest is growing in the potential use of phages to complement antibiotics as a way to fight infection. In 2006, the US FDA and the EU both approved phage preparations targeting *Listeria monocytogenes* on ready-to-eat foods. Currently, phage therapy is part of standard medical practice in the Republic of Georgia and is fairly readily available in Russia, Poland, and other Eastern European countries.

The psychological benefits of human interaction with higher animals like dogs and horses might be explained by our recent coexistence and shared cultural history. The human connection with horses can be traced back even to prehistoric cave paintings. This connection that human beings still subconsciously seek with other living beings has been termed "biophilia" by sociobiologist Edward O. Wilson.

Human-dog partnerships have traditionally provided a service for clients with disabilities, such as the service dogs, which assist people with visual or other physical impairments. Since the first report of a dog as "cotherapist" by American child psychiatrist Boris Levinson in the 1960s, there have been numerous publications outlining the medical and psychological benefits of the human-animal bond. A growing number of practitioners have been integrating animals into their practice, wherein the animal plays an integral role in assisting with the mental health, speech, occupational therapy, or physical therapy goals. When a horse or a donkey is part of the treatment team, it is generally referred to as equine-assisted therapy. Although animal-assisted therapy is well established in many countries, there are numerous exciting avenues still open for research.

A relatively recent example of using animals to help solve medical problems is the application of animals' exquisite olfactory senses to detect illnesses with distinctive odors. For centuries, it has been understood that many human diseases generate characteristic odors. Physicians often recognized the odors associated with conditions such as pneumonia (lung infection), diabetes, and typhoid fever. Dogs have been used by man for their olfactory abilities for many years in the detection of drugs, explosives, banknotes, and other items. Now it has been recognized that dogs may be able to assist in the early detection of human disease, notably various forms of cancer, and hypoglycemic episodes in diabetes.

Each and every biotherapeutic modality discussed in this tome could easily and justifiably be featured in its own volume. Indeed, reviews of several modalities already have been published individually. But biotherapy has seen its rapid advances, in large part, as a result of the multidisciplinary composition of its advocates and researchers. Most biotherapists now recognize that they can learn even more, and advance their own specialties further and faster, by learning about each others' specialties. We biotherapists want to read about the problems that others have faced, and the solutions that others have found. With the publication of this text, the history and current status of the major biotherapeutic modalities finally can be found in one comprehensive yet easily navigated reference book.

The future for biotherapy is bright, exciting, and wide open. Although a lot of work remains to be done, we are confident that all of the modalities described in this volume will become an integral part of conventional medical practice within the near future. The field is advancing quickly, and even as this book is being prepared

for print, new microbes and animals are being studied for their potential value as therapeutic agents. We sincerely hope that this volume will stimulate additional research in biotherapy and will help propel the study and practice of biotherapy even faster and further. Join us, and enjoy the journey.

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# Chapter 1
# Biotherapy – An Introduction

**John C.T. Church**

'Biotherapy' is as old as the hills, in that man has learnt, over the millennia, mostly by trial and error, what the natural world around him has to offer, to alleviate or enhance his condition. By interacting with things, working with them, eating them, or rubbing them on, certain effects will follow, sometimes with dramatic results, including of course, death. As scientists, we divide the natural living world, somewhat arbitrarily, into the plant and animal kingdoms, but these have a massively 'fuzzy' interface. The biological world is diverse, complex, sophisticated and mysterious, changing inexorably over time, so that, whatever we might study or utilise, it is the end result of literally millions, even billions, of years of natural 'research and development'. The 'Bio'- epithet thus is open to a wide range of connotations. A glance at the World Wide Web confirms this diversity of use.

When the International Biotherapy Society (IBS) was founded, at our first conference in May 1996, we defined 'Biotherapy' as 'the use of living organisms in human medicine'. The focus then was primarily on 'Maggot Therapy', 'Hirudothotherapy' and 'Apitherapy'. The emphasis was on utilising the natural abilities, aptitudes and responses of certain organisms, in an environment determined by the practitioner. We were particularly concerned to learn how such organisms would respond to a variety of clinical situations, such as maggots in chronic wounds, and leeches on congested flaps in plastic surgery. Our ideal was to manage the organisms themselves so that they would remain 'happy and hungry', and thereby function optimally, throughout the treatment period, recognising the fact that the environment itself, to which we were subjecting them, might be, or might become, hostile to their wellbeing.

A clinically successful outcome is thus the result of specifically chosen organisms, appropriately prepared for clinical use, introduced to a patient at an opportune time by practitioners who understand the inherent biology of these organisms,

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and can manage the clinical environment to obtain optimal behaviour. This is challenging, and demanding, and is for many practitioners an entirely new concept, but the clinical results can be dramatic and magnificent.

Modern scientific endeavour is essentially reductionist, whereby objects and phenomena are studied at ever increasing depths of detail. Thus, there are now literally hundreds of known elementary sub-atomic particles, with concepts such as 'String Theory' now well established, albeit yet to be 'captured' and 'looked at'. However, the more that is discovered the more there seems to be open for future discoveries. We may know a lot about 'mass' and 'energy', but 'dark matter' and 'dark energy' still comprise 95 % of all that's there! We may have cracked the human genome, but 'non-coding' or 'Junk DNA' is still 98 %!

By complete contrast with all this, and perhaps aimed at the other end of the spectrum of human enquiry and activity, 'biotherapy' is 'holistic'. The term 'holistic' is yet another with a wide scatter of applications. We use it here to define our aim to engage with naturally occurring phenomena and *healthy intact* organisms, in all their diversity and complexity, introducing them into the clinical arena, with the goal of fully *integrating* biotherapy into modern medicine.

Biotherapy is expanding. Our website (www.biotherapysociety.org) now addresses:

**Maggot Therapy**: The use of the larvae of the blowfly *Lucilia sericata* as agents of cleansing or débridement, and enhancement of healing of open wounds.

**Hirudotherapy**: The application of leeches for extraction of blood from congested or inflamed tissues, in a wide range of pathologies.

**Apitherapy:** The introduction of bee venom, by live bees or by injection, for a wide range of chronic ailments. Bee products such as propolis, honey and Royal Jelly are also efficacious, each in its own spectrum of conditions.

**Ichthyotherapy:** The use of certain species of small fresh-water fish as scavenging agents for dermatological conditions such as psoriasis.

**Helminth Therapy:** The use of certain nematode worms as agents for the stimulation of host immunological responses appropriate to the alleviation of certain inflammatory auto-immune bowel diseases such as Crohn's Disease and Ulcerative Colitis. There is the potential use of the schistosomiasis parasite in the prevention of Type 1 insulin-dependant diabetes.

**Phagetherapy:** The therapeutic use of bacteriophages to treat pathogenic bacterial infections (especially those that do not respond to conventional antibiotics) in human as well as in veterinary medicine.

**Animal-assisted therapy:** This type of therapy involves higher animals (mainly dogs and other pet animals) for people with physical, psychological, cognitive, social, and behavioural problems. The special term Equine-assisted therapy is applied when a horse is part of the treatment team.

**Biodiagnostics:** The training of selected dogs to recognise life-threatening medical conditions, such as cancer and diabetic crises, at an early stage, allowing for successful management of the condition by conventional means.

All these aspects of our Society's activities are explained and described in more detail in the appropriate chapters of this book.

Engaging in this way with all these organisms, each with their own particular biology, raises the cogent and attractive question as to whether the active agents, enzymes, cytokines, immuno-stimulants and the rest, that these organisms produce, might be identified and processed by laboratory techniques, to provide us with an enhanced pharmacopoeia. A great deal of study of active agents produced or processed by bees and leeches, has been undertaken. The exo-enzymes secreted by maggots are under active investigation. The volatiles given off by patients suffering from various pathological states, such as cancer and diabetes, are also under scrutiny. 'Sniffer machines' are being developed to recognise specific 'marker' molecules at low concentrations. This must ideally be in collaboration with dogs being trained to identify the chosen 'markers', and the resulting intrinsic specificity fed into the machine programming.

Going down the route towards a 'magical new aspirin' at face value. runs counter to our philosophy of working with intact bio-complexity. A living organism is anything but a tablet. A maggot in a chronic wound will seek out those parts of the wound which provide it with optimal feeding, move relentlessly in the wound in this quest, engage in very efficient group-feeding with other maggots in the wound, produce heat to speed up the wound healing, use oxygen from the air as against from the wound bed, induce the production of cytokines to enhance production of host wound repair cells, produce exo-enzymes appropriate to the type of tissue (skin, fat, muscle) undergoing decomposition, free bacteria from their biofilm, engulf and digest them, thereby increasing its body weight (re-cycling organic waste) 50–80 fold, in 3 days!

There is an aspect of 'biotherapy' not listed above, but which is of fundamental importance to much of modern bio-research and development, and that is the bacterium. Numerous laboratory procedures depend on harnessing selected species of bacteria, and using their natural biology to produce quantities of a given desired product. Their DNA can be altered or added to, to give them further specific laboratory uses. If used in this way to create products of pharmaceutical value, this is a form of biotherapy. But it does not have the *bedside hands-on* aspect that is intrinsic to our other bio-therapeutic protocols.

We mentioned above that biological (natural?) 'research and development' has been active for 'millions of years'. This perforce takes us back to the very first bacterium, with zero antecedents, and enough integrity to withstand a hostile environment perhaps as formidable as that surrounding fumaroles in the deep oceans of today, where certain bacteria are still very much 'at home'. This first bacterium also had to reproduce within hours in order to survive and multiply. From a very early stage, clusters of a mono-culture of these bacteria would then have developed 'quorum sensing' and produced biofilm, with its powerful protective and exclusive attributes. Then such colonies of bacteria would have learnt how to interact with other colonies, themselves protected by their biofilm, and thereby the first multi-cellular organism, of a sort, would have evolved. This phenomenon we now name as a *microbiome*. But, microbiomes interact with other species, for good or ill, and in many ways are controlled by 'host' species, such as insects, that can for instance

preserve in an enclosed sac a mono-culture of organisms to provide them with vitamins.

We have lived for decades with the concept that all microbes are bad for us, and demand ever more powerful *Antibiotics*. We, by contrast, should be looking for new '*Probiotic*' mechanisms, that we can harness, and use in the whole arena of '*Biotic*' control (see for example the chapter on phagetherapy in this volume). We do not necessarily need to know the details of how these mechanisms work, any more than for instance we understand how a dog recognises cancer in a human being, or another dog.

But, we need to have the humility to recognise that nature's answers to the challenges of life, as against our mechanistic modern industrial endeavours, out-class us in most aspects of life. In addition, we need to realise that such mechanisms are ubiquitous, and could be harnessed, using our bio-therapeutic principles central to this adventure, to the enhancement of the well-being of our fellow human beings, the prevention and management of disease, and the nurturing of the environment we all live in.

In summary, biotherapy is challenging and demanding, but it is efficacious, relatively safe, low tech, low cost, and eco-friendly, while properly conducted, it is tremendously rewarding.

# Chapter 2
# Maggot Therapy

**Ronald A. Sherman, Kosta Y. Mumcuoglu, Martin Grassberger, and Tarek I. Tantawi**

## 2.1 Introduction

The use and popularity of maggot therapy (MT) – the treatment of wounds with live fly larvae – is increasing rapidly in many countries throughout the world. The advantages of MT, also called larval therapy, maggot debridement therapy (MDT), and biosurgery, include its profound efficacy in debriding necrotic tissue, its relative safety, and its simplicity. These factors, along with other advantages such as its efficiency, its low cost and its effectiveness even in the context of antibiotic-resistant infections, have been responsible for the recent revival in the use of MT.

The end of the twentieth century witnessed the development of antibiotic resistance to some of the most potent antimicrobials yet created. Ironically (or perhaps as a consequence), the end of the century also witnessed the health care community, once again, embracing the maggot – a creature that thrives in the presence of bacteria, putrefaction and "filth."

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Maggot therapy is often used when conventional medical and surgical treatments fail to arrest the progressive tissue destruction and heal the wound. The poor blood supply to the deep wound and the consequent inability of immunological mediators and systemic antibiotics to reach the infected area prevent healing. For review see: Thomas et al. (1996), Church (1999), Sherman et al. (2000), Mumcuoglu (2001), Nigam et al. (2006a, b, 2010). Internet sites dealing with the subject of MDT are: BioTherapeutics Education and Research (BTER) Foundation; International Biotherapy Society; and World Wide Wounds.

## 2.2 History

For centuries, maggot-infested wounds have been associated with decreased infection, faster healing and increased survival. The beneficial effect of fly larvae for wounds was first observed by Ambroise Paré in the sixteenth century. While working with soldiers wounded and left on the battlefield for several days, Baron Larrey (physician-in-chief to Napoleon's armies) and Dr. Joseph Jones (a medical officer during the American Civil war), both described their observations of maggots cleaning the soldiers' wounds without destroying the viable tissue.

J.F. Zacharias, one of the Confederate Surgeons during the American Civil War, may even have facilitated the deposition of fly eggs on his wounded soldiers (Fleischmann et al. 2004). In non-Western civilizations, the intentional application of maggots for wound healing may date back even earlier (Pechter and Sherman 1983; Church 1996; Whitaker et al. 2007).

The earliest first-hand account of fly larvae *intentionally* applied for wound care was by William S. Baer, Chief of Orthopedic Surgery at Johns Hopkins Hospital in Baltimore (Baer 1929). As a military surgeon during World War I, he too witnessed the beneficial effects of maggot-infested wounds. He treated over 100 children, while observing the effects of maggots on chronic osteomyelitis (bone infection) and soft tissue wounds. He developed practical methods for keeping the larvae on wounds, and documented the mechanisms of action involved, i.e. debridement, disinfection and growth stimulation (Baer 1929, 1931). After witnessing serious wound infections, even in maggot-treated wounds, he concluded that medicinal maggots should be disinfected, and therefore developed methods for chemical disinfection (Baer 1931). Soon thereafter, thousands of surgeons were using Baer's maggot treatment and over 90 % were pleased with their results (Robinson 1935a). The pharmaceutical company Lederle Laboratories (Pearl River, NY; taken over by Wyeth in 1994 and by Pfizer in 2009) commercially produced "Surgical Maggots" until the 1940s for those hospitals that did not have their own insectaries (Chernin 1986).

By the mid 1940s, this treatment modality was abandoned, most likely due to the availability of effective antibiotics. Not only were the antibiotics effective in controlling some of the infections that had previously been treated with maggot

therapy, but most importantly, use of these new antibiotics pre-empted the bacteremia and local spread of infections that previously led to the soft-tissue complications that the maggots so effectively treated. During the next few decades, rare reports of intentional (Teich and Myers 1986) or accidental myiasis (Horn et al. 1976) illustrated the wound-healing benefits of blow fly larvae, when all else failed.

## 2.3 Current Status

The end of the twentieth century was the beginning of a new era for maggot therapy, and for that matter, for most of biotherapy: it marks the first controlled, comparative clinical trials of maggot therapy, which led to regulatory oversight and marketing clearance of medicinal maggots in 2004 by the U.S. Food and Drug Administration (FDA), as the first legally marketed "living therapeutic animal."

In early 1990, a prospective clinical study was conducted to evaluate maggot therapy as a treatment for pressure ulcers ("bed sores") in spinal cord injury patients at the Veterans' Affairs Medical Center in Long Beach, CA (Sherman et al. 1995b). Over the next 5 years, the project was expanded to include other patient populations (Sherman 2002b, 2003). Together, these studies demonstrated unequivocally that maggot therapy was associated with faster and more thorough debridement than conventional surgical and non-surgical modalities. Maggot-treated wounds filled with healthy granulation tissue and became smaller more rapidly than those wounds treated with conventional modalities. Wounds scheduled for surgery or amputation but treated first with maggot therapy required fewer surgical interventions, and those that still required surgery had significantly fewer post-operative infections and wound-closure problems (Sherman et al. 2001; Sherman and Shimoda 2004).

In the two following decades, MT has again become accepted as a wound care treatment. Scores of reports, including clinical trials and basic research, were published in the medical and scientific literature since 1995. In 1995, medicinal maggots were produced in the U.S., Israel and the United Kingdom. By the year 2002, they were being produced by over a dozen labs; by 2011, an estimated 50,000 units were produced by at least 24 laboratories, and shipped to patients in over 30 countries. Today, 20 years after its reintroduction, we estimate that more than 80,000 patients were treated by MT (Mumcuoglu et al. 2012).

More recently, MT is taught in medical and surgical training programs, and medical device companies are investing in maggot laboratories, dressings and research. The growing acceptance of MT is due mainly to the growing need for effective, low cost wound care, combined with the growing recognition that maggots can provide exactly that: simple, safe, effective and low-cost wound care (Wayman et al. 2001; Thomas 2006).

## 2.4 The Fly

Medicinal blowfly maggots are selected for their ability to feed on dead tissue without disturbing viable tissue (Sherman 2002a). The most commonly employed larvae have been those of the green bottle fly, *Lucilia sericata* (or *Phaenicia sericata*, depending on authority) (Fig. 2.1).

Rarely, therapists have used related species, such as *Lucilia cuprina* and *Calliphora vicina* (Table 2.1); but these have not been studied as extensively (Paul et al. 2009; Tantawi et al. 2010; Kingu et al. 2012).

*L. sericata* is common all over the temperate and tropical regions of the world. It prefers warm and moist climates and accordingly is especially common in coastal regions. The female lays her eggs (up to 200 during her lifetime) on decaying organic material such as feces and animal corpses. Depending on external temperatures, the eggs hatch within 8–24 h, releasing larvae. The larvae will molt twice over the course of 4–7 days (again, depending on temperature). After the third stage (instar) of their larval period (Fig. 2.2), they will wander away from the host and enter their pupal stage. The pupal stage lasts approximately 10–20 days, at the end

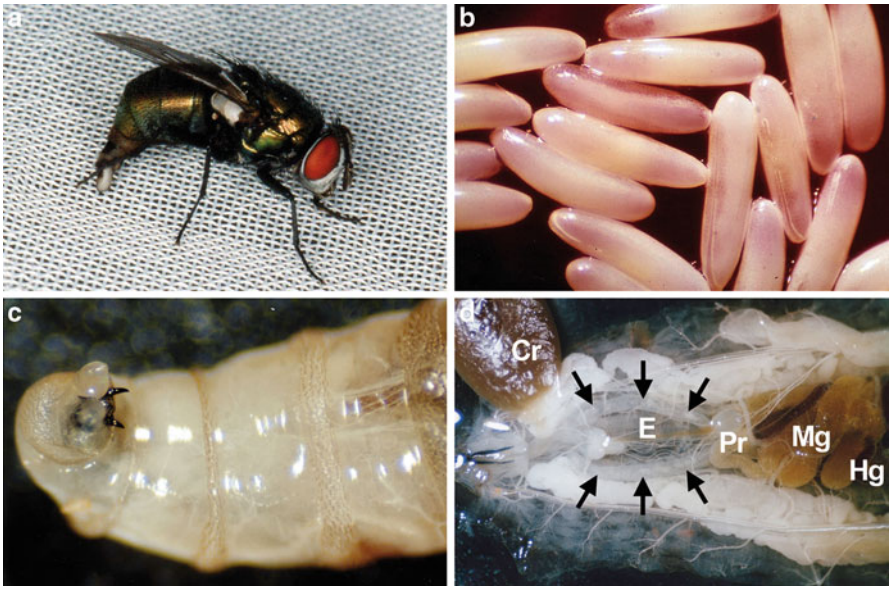


**Fig. 2.1** The green bottle-fly, *Lucilia sericata*: (**a**) Female fly with visible ovipositor; (**b**) eggs; (**c**) apical part of a grown third instar larva with the two protruding mouth hooks; (**d**) dissected third instar larva with paired large salivary glands (*arrows*), the crop (*Cr*) rotated to the *top left*, esophagus (*E*), proventriculus (*Pr*), the *light-brown* midgut (*Mg*) and beginning of the darker hindgut (*Hg*). The large *white* masses on the *upper and lower part* of the picture are the larval fat bodies

**Table 2.1** Species of flies used in maggot therapy

| Family | Species | References |
|---|---|---|
| Calliphoridae | *Calliphora vicina* | Teich and Myers (1986) |
| | *Chrysomya rufifacies* | |
| | *Lucilia caesar* | Baer (1931) and McClellan (1932) |
| | *Lucilia cuprina* | Fine and Alexander (1934) |
| | *Lucilia illustris* | Leclercq (1990) |
| | *Lucilia sericata* | Baer (1931) |
| | *Phormia regina* | Baer (1931) |
| | | Horn et al. (1976) |
| | | Horn et al. (1976) |
| | | Robinson (1933) |
| | | Reames et al. (1988) |
| | *Protophormia terraenovae* | Leclercq (1990) |
| Sarcophagidae | *Wohlfahrtia nuba* | Grantham-Hill (1933) |
| Muscidae | *Musca domestica* | |

References indicate the first known use of a specific fly species for this purpose

**Fig. 2.2** Third instars of *Lucilia sericata*

of which the organism will have transformed (metamorphosed) and emerged (eclosed) as an adult fly (Greenberg 1973) (Fig. 2.3).

At higher temperatures (37 °C) the newly hatched larvae enter their pre-pupal stage within 48 h.

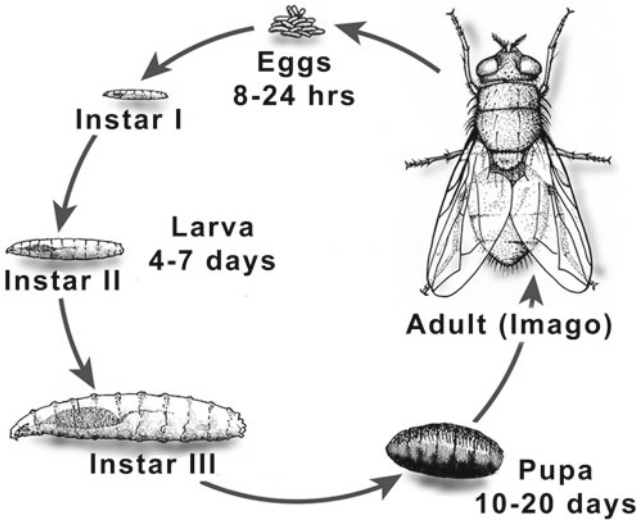


**Fig. 2.3** The life-cycle of *Lucilia sericata*

## 2.5 Mechanisms of Action

The following mechanisms of action have been observed:

### *2.5.1 Debridement*

The most obvious benefit of maggot therapy is the ability of medicinal maggots to effectively debride wounds by removing the sloughy, necrotic tissues. This process is accomplished both physically and chemically. Extracorporeal digestion by the maggots' proteolytic enzymes is one mechanism by which wounds are cleaned. Secreted collagenases and trypsin-like and chymotrypsin-like enzymes have been described (Vistnes et al. 1981; Chambers et al. 2003; Horobin et al. 2003, 2005).

Each maggot is capable of removing 25 mg of necrotic material within just 24 h (Mumcuoglu 2001) (Fig. 2.4).

Maggots secrete their digestive juices directly into their environment, and these proteolytic enzymes are largely responsible for removing the infected, dead tissue from the wound by liquefying the tissue into a nutrient-rich fluid that can be imbibed by the maggots. These proteases may be the vehicle by which the maggots precipitate other wound healing effects, as well. Proteolysis is involved in tissue repair, haemostasis, thrombosis, inflammatory cell activation and tissue reconstruction. Proteinases (mainly matrix metalloproteinases, such as the serine proteases)

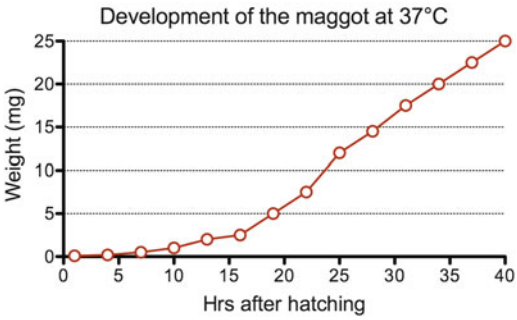


**Fig. 2.4** Increase in weight of the *Lucilia sericata* larvae at 37 °C

are involved in collagen degradation, keratinocyte migration, and activation of endothelial cells, fibroblasts, keratinocytes and platelets, through proteinase-activated receptors (Chambers et al. 2003; Brown et al. 2012; Pritchard et al. 2012; Telford et al. 2012).

In addition to the serine proteases, two other classes of proteolytic enzymes are also present in *L. sericata* larval secretions (Chambers et al. 2003); but the predominant activity belongs to the trypsin-like and chymotrypsin-like serine proteases. All together, the larval proteinases are active across a wide pH range (pH 5.0 to pH 10.0).

In addition to enzymatic debridement, maggots also exert a physical debridement over the wound bed (Barnard 1977; Thomas et al. 2002). Blow fly larvae are covered by spines and two mouth-hooks, which aid in locomotion. As the maggots crawl about the wound, these rough structures loosen debris just like a surgeon's "rasper."

### *2.5.2 Disinfection*

Since the natural habitats of blow flies are corpses, excrement, wounds, and similar decaying organic matter, it is obvious that they must be resistant to microbial attack. With the work of William Baer (1931), the antimicrobial activity of maggots began to be appreciated. Early theories were that the maggots killed bacteria through ingestion (Livingston and Prince 1932; Robinson and Norwood 1933, 1934). Greenberg (1968) demonstrated bacterial killing within the maggot gut, and provided evidence that the activity was due, at least in part, to metabolic products of *Proteus mirabilis* (a commensal gram-negative bacterium within the larval gut. Erdmann and Khalil (1986) went on to identify and isolate two antibacterial substances (phenylacetic acid and phenylacetaldehyde) produced by *P. mirabilis* that they isolated from the gut of screwworm larvae (*Cochliomyia hominivorax*).

Mumcuoglu et al. (2001) added to our understanding of alimentary disinfection, and demonstrated that *P. mirabilis* is not required for the process, by feeding green fluorescent protein-producing *Escherichia coli* to *L. sericata*, and using a laser

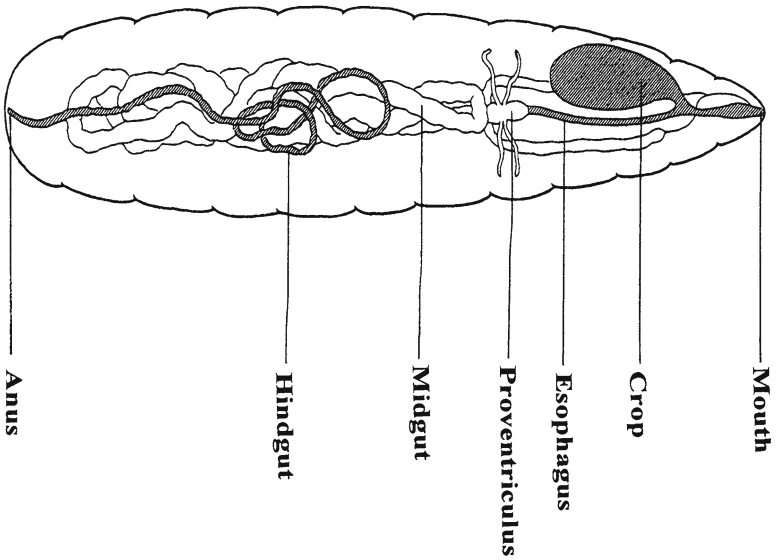


**Fig. 2.5** The digestive tract of maggots from *Lucilia sericata*

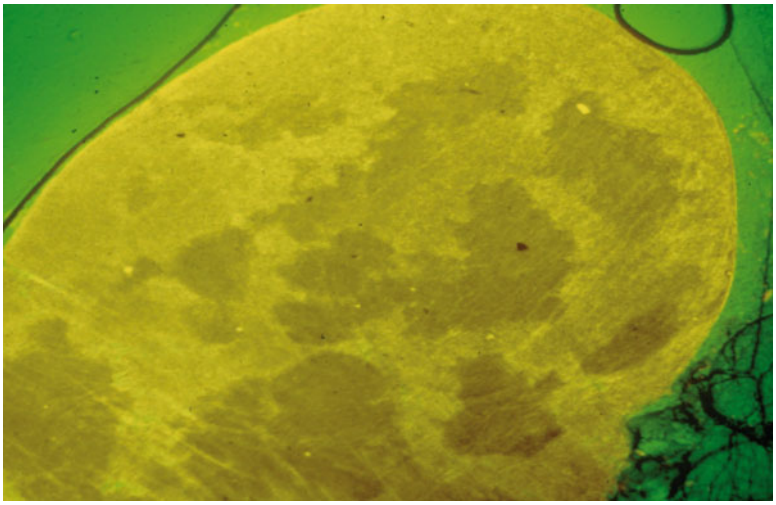

**Fig. 2.6** The crop of the maggot packed with large numbers of fluorescent *Escherichia coli* bacteria

scanning confocal microscope to detect the fluorescence as the bacteria traveled through the maggot's gut (Fig. 2.5). The number of bacteria, very high in the crop (Fig. 2.6), decreased significantly in the mid- and hindgut, with essentially no bacteria reaching the end of the gut (anus) (Fig. 2.7).

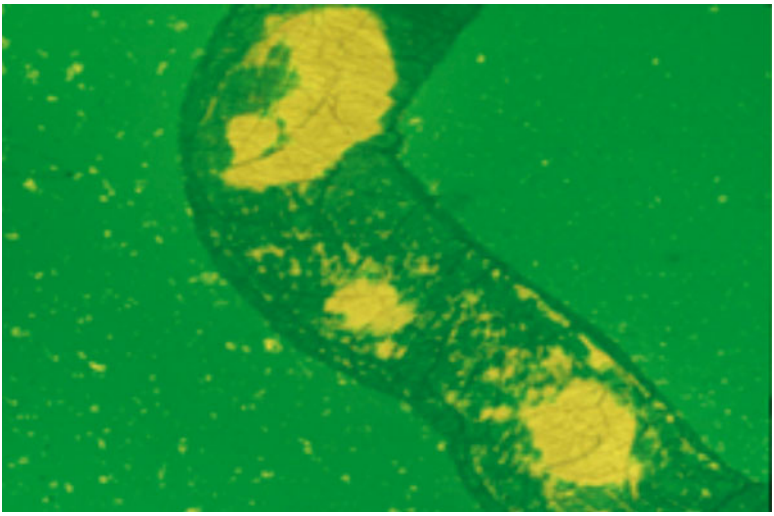

**Fig. 2.7** The hindgut of the maggot with decreased numbers of fluorescent *Escherichia coli* bacteria

Antimicrobial killing also occurs outside the maggot gut in the wound bed itself. Some early researchers pointed to the fact that the profuse exudates might be washing the bacteria out of the wounds. Changes in the alkalinity of the wound were also felt to be a mechanism of bacterial killing (Baer 1931) as well as the ammonium products themselves (Messer and McClellan 1935; Robinson and Baker 1939).

Simmons (1935) and Pavillard and Wright (1957) demonstrated that excretion of the antimicrobial gut contents was probably the major mechanism by which the maggots were killing bacteria even before ingesting them.

A preliminary study demonstrated that sterile *L. sericata* secretions exhibit marked antimicrobial activity against liquid cultures of the Gram positive *Streptococcus* sp., *Staphylococcus aureus* and a clinical strain of methicillin-resistant *S. aureus* (MRSA) (Thomas et al. 1999).

Bexfield et al. (2004) and Kerridge et al. (2005) isolated two antibacterial fractions from maggots of *L. sericata*; one with 0.5–3.5 kDa and the second <500 Da. It was shown that these antibacterials are active against a range of bacteria, including the Gram positive *S. aureus*, both methicillin-resistant *S. aureus* (MRSA) and methicillin-sensitive *S. aureus* (MSSA), *Streptococcus pyogenes* and, to a lesser extent, the Gram negative *Pseudomonas aeruginosa*.

Huberman et al. (2007b) isolated three molecules with a molecular weight (MW) of 194, 152 and 138 Da, having antibacterial activity. The antibacterial activity was observed in extracts of whole body, haemolymph and in the excretions of the maggots, and it was effective against a large number of pathogenic and non-pathogenic bacteria (Huberman et al. 2007a). By examining the influence of an infected environment and physical injury on maggots, it was found that the activity was higher in non-sterile