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The Israel Chemist and Chemical Engineer

ICE

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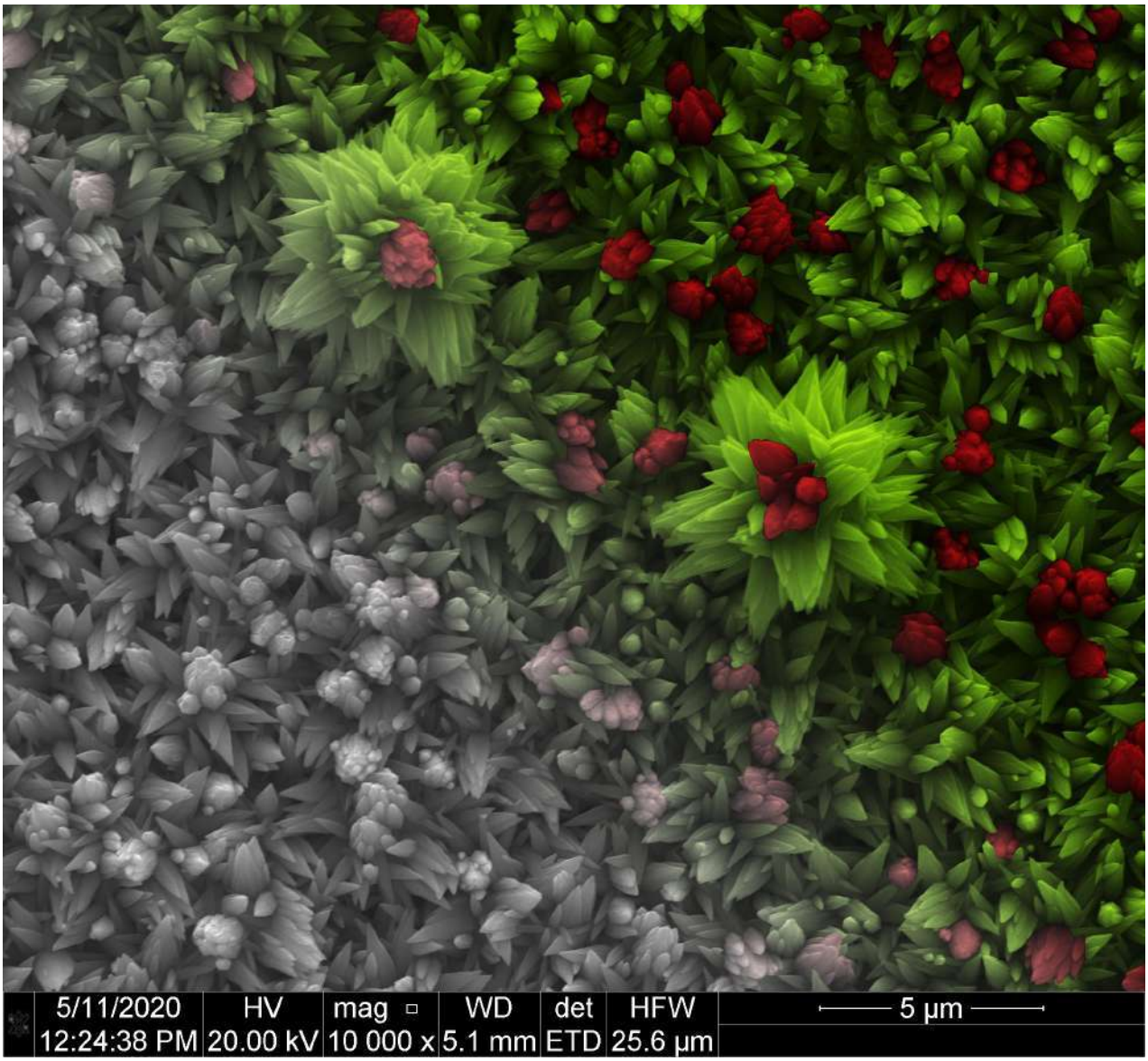

The Israel Chemical Society
(ICS: www.chemistry.org.il)

Editorials

Scientific Article

History of Chemistry Articles

Profile

Front cover: "Flowering of ZnO" an E-SEM image of ZnO surface by Eitan Edri, a final-year PhD student in Hagay Shpaisman's group at the Department of Chemistry, Bar-Ilan University

Dear Readers,

Welcome to the seventh issue of the Israel Chemist and Engineer (ICE) online magazine, a publication of the Israel Chemical Society (ICS). We hope you will find the magazine interesting and will be inspired to contribute to future issues.

In the last issue, Bob Weintraub wrote about Jonas Salk and the first vaccine against polio. As the corona pandemic is unfortunately not yet over, although the emerging vaccines have given us some reason for hope, he has contributed another article on vaccines, this time about Baruch Blumberg who discovered the hepatitis B virus, diagnostic methods for its detection and a vaccine for it. Arnon Shani, a former President of the ICS, brings us a fascinating article on the effect of insect sex life on the world economy. We also have an interesting article on the use of vacuum technology in the extraction of cannabinoids, and an intriguing account of the relationship between Fritz Haber and Chaim Weizmann. We are also republishing the late Asher Mandelbaum's account of his life in Europe during World War II. To conclude, we have an interview with the medicinal chemist and raconteur Abraham Nudelman, together with one of his stories of famous chemists.

If you have suggestions for future editions, comments on the current issue, or would like to contribute an article, please contact me at gordon@biu.ac.il.

Arlene D. Wilson-Gordon
Professor Emerita
Chemistry Department, Bar-Ilan University
ICE Editor

Dear Colleagues,

The year 2020 will be remembered by most of us as a challenging experience, and it seems that the COVID-19 pandemic with its consequences will stay with us for quite some time, affecting every aspect of our life. We, and most other scientific communities operate in a survival mode, hoping that life will get back as good as possible to the pre-Corona times.

We were fortunate to hold our 85th Annual Meeting last February in Jerusalem, just before most countries closed their borders, universities, and schools, sending their scientists and students to home confinement. We were also fortunate to host an extraordinary delegation of professors and graduate students from Yale University, and the ACS President. Remarkably, since the establishment of the ICS in 1933, we have kept the tradition of Annual Meetings with virtually no interruption.

Unfortunately, we need to skip an Annual Meeting for the first time in the 87 years of ICS history, postponing the 86th Meeting from February 2021 to February 2022, when we will host a delegation from Peking University and the Chinese Academy of Sciences. Profs. Charles Diesendruck and Saar Rahav of the Technion's Schulich Faculty of Chemistry have taken responsibility for chairing the meeting. Nevertheless, we will hold the ICS Award ceremony this year on May 6th, 2021, at the Open University.

We should also remember the upside of our activities. We have recently established the ACS Israeli Chapter, which will benefit the Israeli chemistry community on multiple levels. The ongoing collaboration between the ICS and ACS includes several joint activities, such as ACS-ICS joint symposia at the ACS National Meetings. The next one, dedicated to C1 Chemistry, will take place at the 2021 Fall Meeting. Excellent news comes from our high schools: the number of pupils who studied chemistry at the 5-point level has increased from about 7,000 in 2011 to over 11,500 last year. We hope that these numbers will translate into increased enrollment in chemistry in the higher education system.

The ICS has significantly enhanced its participation in international organizations, including EuChemS, IUPAC, and the Federation of Asian Chemical Societies (FACS). I am proud of my service on the IUPAC Bureau for two terms and my service as the Communications Director of the FACS. I am pleased to serve as an Editor-in-Chief of the FACS new, free-access magazine, AsiaChem, and I invite you to read the inaugural issue: https://www.facs.website/november-2020.

We have also bolstered our scientific journals, the Israel Journal of Chemistry (IJC, published by Wiley-VCH) and Physical Chemistry Chemical Physics (PCCP, published by the Royal Society of Chemistry). I encourage all of you to contribute to these journals. If you consider serving as a Guest Editor of one of the IJC future issues, please contact me directly.

Following the recent elections to the ICS institutions, I welcome the new board members and thank those who have completed their service on the board. As ICS President at a difficult period, I start my fifth term with much hope and optimism, looking forward to the post-pandemic times.

Finally, I am delighted to see this ICE magazine's development under Editor-in-Chief, Prof. Arlene Wilson-Gordon of Bar-Ilan University. I encourage you to contribute an article to the ICE on any topic you like, including popular science, history of science, report on an event, opinions, etc.

Enjoy your reading,

Ehud Keinan
President, the Israel Chemical Society

The effect of insect sex life on the world economy; Evasion of mating disruption with sex pheromones in insect pest control

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Abstract

This article deals with pheromones, animal chemical communication materials, based on popular public lectures, on the one hand, and chemical and biological information on the other. The last part of the article was written recently as the result of fresh news from the field, which affirmed my working hypothesis regarding evasion of mating disruption. I have chosen to present the topic through a Q&A, focusing on the topics that are often raised by listeners or other interested parties.

Q: There are two titles and so there are two questions: Is the first title a publicity stunt or is there something real hidden behind it? The second relates to the application. Could you please elaborate?
A: As for the first one, the relationship is very close and this is the heart of the article. Every word is essential. The second one is the highlight of my studies and it will be explained in the last part of the article.

Q: So, what is the connection between insect sex life and the world economy?
A: The connection is in pest control in general, and in agriculture, in particular.

Q: How are these materials used for pesticides?
A: To understand this, you must understand the significance of chemical communication between animals, in general, and insects, in particular, that are the major pests in agriculture.

Q: What does "chemical communication" mean?
A: Chemical communication is part of the information transfer system between animals, including humans. As is well known, there are five senses for transferring information between animals (also between animals and plants). Two senses are physical senses – the sense of hearing and the sense of touch. Two senses are chemical senses – the sense of taste and sense of smell, based on the interaction of molecules with receptors in the corresponding organs (mouth, tongue; nose). The sense of vision is a combination of a physical process (in the beginning) and a chemical process (thereafter).

Q: Is it possible to place all the communication chemicals in one group, or are there different categories?
A: All chemicals used to transmit information are called semiochemicals or infochemicals.

Prof. Arnon Shani is an Emeritus Professor in the Chemistry Department at Ben–Gurion University of the Negev. He received his MSc degree at the Hebrew University of Jerusalem with Prof. A. D. Bergman and his PhD at the Weizmann Institute with Prof. P. Sondheimer. After a postdoc in Chicago University, he joined the research group of Prof. Rafael Meschulam's at the Jerusalem School of Pharmacy. In 1968, he joined the four founders of the Chemistry Department at the five-years-old Institute of Higher Education in the Negev, which later became Ben–Gurion University of the Negev. Arnon held many senior positions at Ben–Gurion University, as well as nationally and internationally. He served as President of the ICS from 1997–2003 and was appointed an Honorable Member of the ICS in 2014.

Q: We know ingredients that are pleasant or repellent, sweet or savory and more flavors. Do they all belong to this category?
A: We will first distinguish between taste and smell (sometimes there is a connection between the two senses). Flavorings are mainly related to food. The pheromones are odorants and we will focus on them. There are indeed different groups of such substances, but we will distinguish between chemicals used by individuals of the same biological species and those used for communication between individuals of different species. The chemicals in the second group are called allelochemicals and we will not deal with them in this article. The chemicals in the first group are *pheromones* [1]. These are a secreted or excreted chemical factor that triggers a social response in members of the same species, resulting in a change in their development or behavior. The term pheromone derives from two Greek words: pherein – to carry, and hormone.

Q: I see that the word hormone appears in the concept of pheromone. What is the connection?
A: Both pheromones and hormones are chemical "messengers", that is, secretions that transmit information or instructions to living systems. However, the hormones are in vivo communicating substances, that is, between organs in the same living body, while the pheromones are in vitro communicating substances, between different individuals of the same biological species.

Q: You consistently mention pheromones in the plural. What is the reason for this?
A: The information that needs to be transferred between individuals is vast and diverse, and in order to distinguish between types of information and their purpose, there is a need for a number of pheromones, different from one another, to transfer the appropriate information for a particular action. We define pheromones in various roles, for example:
Alarm pheromone – warns individuals in the population of imminent danger;
Aggregation pheromone – gathers the whole population (males and females) together whether for roaming (like locusts) or for finding food;
Territory pheromone – marks a living area (most commonly found in mammals, such as dogs and large carnivores);
Sex pheromone – attracts a mate for mating and fertilization purposes. This pheromone, which is most essential for biological existence, is mistakenly considered by many to be the same as all pheromones, and the predominant view is that pheromones are just sex pheromones. Of course, this is not true. We will return to the topic of pheromone specificity, in general, and the sex pheromone in particular.
Trail pheromone – marking a trail for various purposes, for example, by ants transporting food to the nest, or when roaming from nest to nest.

Q: Wait, is that all or are there more pheromones?
A: As I mentioned, there are different and varied messages, so there are more pheromones such as the pheromone of home recognition, the pheromone to prevent laying of eggs, the queen's pheromone (in the hive, for example, to allow the queen to control all the thousands of workers), the pheromone for removing dead bodies (after battles between nests of termites or ants). Undoubtedly, there are other undiscovered pheromones.

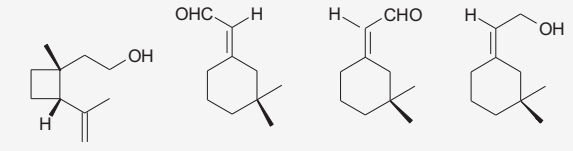
Q: From what you say, one can understand that pheromones are used for chemical communication between animals. Does the entire animal kingdom use them?
A: Yes indeed. As we know today, not only animals but also algae use sexual contact materials for fertilization, as do bacteria and other microorganisms, fish, various sea creatures, insects, spiders, amphibians, reptiles, and of course mammals.

Q: Do you mean humans too?
A: Certainly, there is an effect of chemicals on our behavior, and there may even be a sex pheromone, but the issue is still not definitively "closed" and there are various opinions on the subject. The organ responsible for sensing the sex pheromone in the high mammalian olfactory system probably degenerates in humans, so what remains is a remnant of a system that may have worked in the past. Other senses probably play an important role in the sexual connection of humans. What is clear is that women living together (nuns, student dormitories) within a short period of time begin "coordinating" (synchronizing) their menstrual period (also found in mice). But, let us return to the subject of pheromones and their properties.

Q: Indeed, an impressive variety. Do all pheromones have the same or different chemical components?
A: This is one of the unique and interesting phenomena – the pheromone is usually a mixture of several substances in a relatively constant ratio (although not uniform between all individuals), and is unique to each species. That is, the number of different molecules, used as pheromone components in one species, could reach ten or even more in several of the pheromones mentioned above.

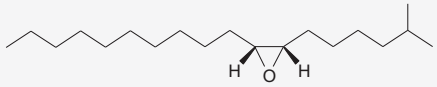
Q: You mention that there are different chemicals. Maybe you can give an example of pheromones?
A: The pheromone ingredients are very varied and include substances from different families ranging from saturated hydrocarbons, through unsaturated, chain or ring, long chain alcohols, their acetates, aldehydes, aromatic substances, heterocycles, amino acid esters, steroid derivatives, terpenes, short peptides, and more (see Scheme 1).

Scheme 1. Examples of pheromones and their components



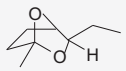
(1R,2S)-(+)-Grandisol
Ratio: 6 1 2 6

Grandlure, aggregation and sex pheromone released by the male boll weevil (*Anthonomous grandis*).



(7R,8S)-(+)-cis-epoxy-2-methyloctadecane

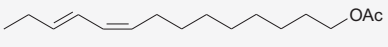
Disparlure, sex pheromone released by the female gypsy moth (*Lymantria dispar*).



(1R,5S,7R)-(+)-exo-brevicomin

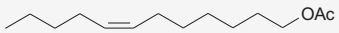
(1S,5R)-(-)-frontalin

Aggregation pheromone of the western pine beetle (*Dendroctonus brevicomis*) released by females (brevicomin), males (frontalin) and the tree (Myrcene).



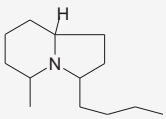
(Z,E)-9,11-tetradecadienyl acetate

Prodlure, the main component of the sex pheromone released by the female Egyptian cotton leafworm (*Spodoptera littoralis*).



(Z)-7-Dodecenyl acetate

The sex pheromone released by the female Asian elephant



all-cis-5-methyl-3-butyloctahydroindolizine

Monomorine I, a component of trail pheromone released by Pharaoh's ant (*Monomarium pharonis*) and related species.

Q: What else characterizes pheromones?
A: The most important feature is its uniqueness – that is, each biological species has its own pheromones, and they usually do not interfere with or affect other species. This is extremely important in the sex pheromone, to prevent the attraction of mates between different, but closely related species, which could lead to unwanted hybridization. Unlike chemistry, which prefers hybrid orbitals, biology doesn't like hybrids of different species. Thus, even closely related species have their own unique pheromones. This can be seen in Table. 1, where we list the composition of sex pheromones of closely related species. The structure of the chemicals also shows us which molecules are commonly found in the pheromones of moths, which are devastating pests in agriculture.

Q: If you are mentioning agriculture, what are the major pests?
A: Food crops, industrial crops (cotton), forests for the timber industry – all of these are severely affected by moths (night butterflies), beetles and flies. It is estimated that about one–third of the crop is damaged in the field, and another 10% is damaged in harvesting, packaging and marketing, so that almost half the crops are damaged before reaching the consumer. From now on, I will concentrate on moths and their sex pheromones.

Table 1. Different relative composition of sex pheromones in closely related moth species

The biological species	Relative components of the pheromone			
	cis–11–C_{14}OAc	trans–11–C_{14}OAc	cis–9–C_{14}OAc	C_{12}OAc
Archips agryrospilus	60	40	4	200
Archips mortaunus	90	10	1	200
	(cis,cis)–7,11–C_{16}OAc		(cis,trans)–7,11–C_{16}OAc	
Pectinophora gossypiella	1		1	
Pectinophora endema	1		0.5	
Pectinophora scutigera	1		0.1	

Q: Why moths?
A: For several reasons: First, the larvae of the moths are the most severe pests and they have developed significant resistance to conventional pesticides (organochlorines such as DDT), organophosphates (such as parathion), carbamates, pyrethroids, nicotinoids and more.

Second, sex pheromone components in moths belong to a well–defined and relatively easy group of chemicals: derivatives of fatty acids i.e., alcohols with a chain length of 10 to 18 carbon atoms with one, two or three double bonds in cis and trans configurations at different locations along the chain length, and acetates and aldehydes derived from these alcohols. There are of course other derivatives, such as epoxides. Third, it is relatively easy to grow these insects in the laboratory, enabling continuous research throughout the year. For these reasons, it is clear why the number of pheromones currently identified is mainly in this group of insects. If, in the early 1960s (when pheromone research first become popular), the structure and composition of pheromones of only a few moths was known, today more than a thousand are known.

Q: What else can be said about moth sex pheromones?
A: Beyond their uniqueness, their high sensitivity is next in line. Controlled laboratory experiments show that the amount required for a male moth to start looking for a female moth,

which secretes the sex pheromone, is about 10^{-18} grams per cubic centimeter, which is a few thousand molecules, enough to stimulate the male to sexual attraction and looking for the female. The pheromone produced in the female moth gland turns out to be in the range of nanograms or less. Table 2 summarizes some quantitative data.

Table 2. Quantities of sex pheromone isolated from female moths

Biological Species	No. of females	Extracted(mg)	ng/female
Almond moth	1,200,000	6.1	5.08
Indian meal moth	335,000	0.5	1.49
Mediterranean flour moth	283,000	0.8	2.83
Tobacco moth	1,313	0.0024	1.83

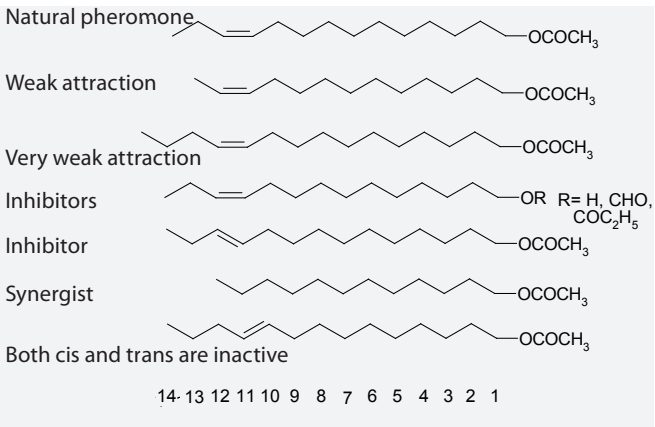
The enormous differences in the biological activity of the silkworm moth pheromone isomer series, shown in Table 3, demonstrate the high specificity of the pheromone structure.

Table 3. Comparative attraction of sex pheromone in silkworm moth and its isomers

Tested isomer	Attractivity (µg/ml)
Natural pheromone (trans–10, *cis*–12–hexadecadienol)	10^{-10}
Cis–10, *cis*–12–hexadecadienol	1
Cis–10, *trans*–12–hexadecadienol	10^{-3}
Trans–10, *cis*–12–hexadecadienol (synthetic)	10^{-12}
Trans–10, *trans*–12–hexadecadienol	100

Scheme 2 further illustrates the uniqueness of the structure and its effect on biological activity. Extending the hydrocarbon chain by one carbon atom, moving the double bond, changing from cis to trans, or changing the ester group – all severely impair biological activity.

Scheme 2. Comparing activity (quality) – male attraction of red banded leaf roller moth to different chemicals



These tiny quantities, which are actually a mixture of a few ingredients, made it difficult to research pheromones at the beginning. The idea of volatile chemicals being used for remote sexual attraction among insects was already known in the 1930s, when moth females in traps were used in Czechoslovakia to attract and detect the harmful moths: the males were attracted to the females so that the farmers knew if the pest was actually in the plantation or in the field, and, if so, in what quantity and in what areas. This method – the monitoring method – is currently widely used in areas of vegetables, cotton fields, orchards, forests and other crops.

Q: Why did you note that "these tiny quantities made it difficult for pheromone research to get started"?
A: It was not until the 1960s that gas chromatography became practical and widely used in organic chemistry research. Sensitivity was then low and relatively high concentrations were required but, nonetheless, micrograms concentrations could be detected. It was only in the 1980s that the nanogram (or even less) sensitive devices began to appear. In 1988, I measured quantities of pheromone components from one female moth gland that reached 20–50 picograms (10^{-12} grams).

Q: I'm sorry to interrupt you, but from when are the pheromones known?
A: Only briefly, because I do not want to deviate from the main topic. Well, in the 17th century scientists investigated the behavior of ants and noticed the well–known phenomenon of walking in a food–gathering column, or moving from nest to nest, for example, and assumed that there were components that allow ants to follow one another. Another finding was reported in the 1870s by the French pastor Faber, whose hobby was butterfly breeding. He showed that the antenna of the butterfly is the "smelling" organ and that males are attracted to females for mating. The scientific report on the first identified pheromone, a sex pheromone of the silkworm moth, the silkworm we raised on mulberry leaves when we were children, was published in 1959. Since then, there has been a real surge in pheromone research, ranging from the isolation and characterization of the pheromone components, their synthesis to prove structure and application requirements, studying the pheromone biosynthesis process based on the genetic and hormonal control of the process, the sensing of the pheromone in the antenna and the electrophysiological processes derived from it, the enzymatic metabolism and exclusion of the products from the receptors, and a simple way to apply pheromones in pest control, and all that entails. In these studies, biologists, chemists, ecologists, pesticides production and farmers are all involved.

Q: You mentioned the use of pheromones for pest monitoring purposes. What exactly do the traps trap?

A: Before answering your question, just a short explanation: As you know, insects usually have four stages in their life cycle: egg, caterpillar, pupa and adult. Such a cycle can be seen in the series of pictures of the beetle Meladera matrida, known in Israel as "Khomeini", which is a species new to science (Figure 1). Usually, the adult is responsible for fertilization and reproduction, so the sex pheromone is secreted by the adult (male or female) to attract the other mate. By monitoring the population of the adult of the specific pest (ensnaring the adults by attracting them with the sex pheromone in traps), one can get crucial information about the size of its population, its spreading in the field and when to treat it. This information answers the big W questions: When, Where, What and hoW much to spray of the pesticide.

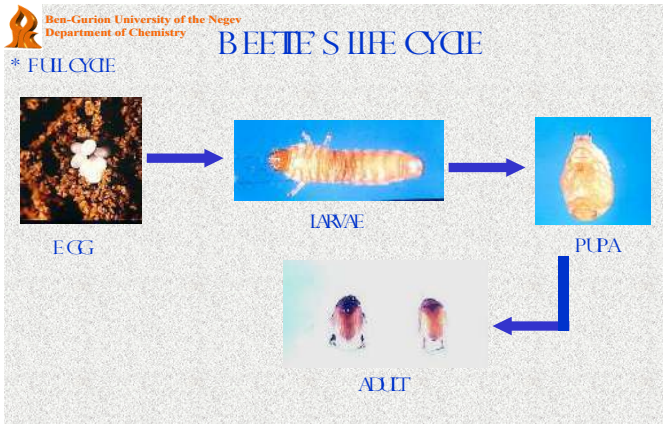


Figure 1. The life cycle of the beetle Maldera matrida, a new species to science discovered in Israel

Q: How does the adult moth find its mate?
A: A change in the amount or concentration of pheromone in the air enables the moth to locate the pheromone source. A female moth that secretes the sex pheromone protrudes from the end of her abdomen (where the tiny pheromone gland is located, sub–mm in size, which produces and secretes the pheromone), so that wind and air currents absorb the pheromone components and transport them. Using the antenna, the pheromone molecules are detected and the male begins to fly upwind, against the airflow, and feels a growing concentration of pheromone in the air. To make sure, they fly in a zig–zag track, and sense the concentration changes in the air at varying altitudes. One can describe this flight as conical with the apex pointing at the source, where the pheromone originated, tens and hundreds of meters away. In this way, they navigate their path until they reach the source and find the female calling them.

Q: If I understood correctly, disruption of the pheromone concentration in air could interfere with the male locating the female.

A: Great point. Indeed, the effective way of damaging the chemical communication between males and females is by artificial "saturation", relative to the pheromone concentration in the air. I shall come to this later.

Q: Is that why both the first and the second titles of the article are as shown above?
A: Indeed, it is. The component of sex life is already clear, and the economic component stems from the fact that pesticides to control insects (insecticides) are used every year at a cost of $8–10 billion. Millions of tons of these materials are sprayed in fields, orchards and forests each year. We breathe and eat these harmful pesticides that contaminate the environment, harm natural enemies and beneficial insects, and undermine biological equilibrium. Most of all, the pests develop resistance to these insecticides. This resistance reduces the effectiveness of the materials, necessitating a constant search for new and effective materials (in many cases toxicity also increases). This open–ended research process requires the investment of hundreds of millions of dollars to introduce one new pesticide into the market after ten years of research and examination of about 15,000 new chemicals. The result is that the number of new chemicals entering the field every year is decreasing. In addition, governments and environmental authorities mandate a reduction in the use of toxic pesticides. These have all led to the advanced approach of integrated pest management (IPM), or integrated protection, which employs all means to protect the crop from pests. In this power game, the pheromones have a wide range of possible applications, and some of them are already in use.

Q: It is now clear to me that there is no advertising trick here and there is a reason for every word. We will now return to the pheromone topic. You cited the "confusion" method as a way of pest control. Can you expand?
A: Remember, the male locates the calling female according to the change of concentrations in the air. If we create a state in which the concentration in the air is uniform and constant, and higher than the natural concentration that results from its spread by the female (as established in moths), the males will not be able to locate the pheromone source and will not know where to fly and look for the females.

Q: It sounds very simple.
A: True, like many ingenious things that are simple, so is "confusion." Properly applying and releasing enough sex pheromone of a specific moth, seems to prevent sexual encounter between the mates, and the level of interference in communication reaches about 98–99%, which means almost complete prevention of fertilization. The result is that the amount of fertilized eggs laid in the field is extremely low and the level of pest population in the next generation is extremely low, and the level of damage to the crop is low as

well. This allows the farmer not to spray pesticides (or very little), because the expense of spraying is higher than the damage caused by the pest.

Q: That sounds nice, but what is the cost of applying the pheromone preparation in the field?
A: Calculations and actual testing by the farmers show that the cost of the pheromone preparations is the same as the cost of pesticides, so it is economically worthwhile. In addition, there are farmers who are interested in organic farming, without using pesticides, even if the cost is higher, because the value of "green" produce is higher. Thus, from every angle, the method is affordable. If we add the environmental aspects then it is important to apply pheromones in pest control.

Q: Are there any other benefits of pheromones that you don't mention?
A: The most convenient way is to present the properties of the pheromones versus those of conventional chemical pesticides, as we see in Table 4. If we go through each section, individually, we can find the benefits and differences and answer them.

Table 4. Characteristics of pest control based on insect sex pheromone compared with conventional insecticides

Pheromones	Insecticides
Selectively eliminate harmful insects	Eliminate insects non–selectively
Do not disrupt biological equilibrium (partial elimination)	Disrupt biological equilibrium (eliminate most insects)
Do not pollute the environment	Cause severe environmental pollution
Nontoxic	Toxic to man and other animals
Unstable, decompose in the field	Some are extremely stable
No resistance mechanism observed since this would lead to suicide. Insects may develop evasion.	Lead to development of resistance
Minute amounts required; dose for attraction of a single insect 10^{-18}–10^{-15} g	Very large amounts needed; dose for elimination of a single insect 10^{-6} g
Development moderately expensive	Development very costly

Q: I see that you indicate that "resistance" is unlikely to develop and emphasize that this is a "suicide" act. What does that mean?
A: In order to explain the topic, which is very basic in science, it is necessary to understand that the resistance to sex pheromones means that no attraction between the mates will occur. Instead, the insects will find a way to evade the effect of "excess" pheromones. We know that every action in nature draws a response, not only in physics but also in all life processes and environmental factors.

If we focus on pesticides for insect control (including anti–bacterial and drugs included in this explanation), which are actually poisonous substances to the living organism, we know that over the years (usually within 5–6 years), a pest population develops resistance and is no longer affected by the pesticide. The process or mechanism employed is based on the insect's biochemical–enzyme ability to neutralize pesticides or remove them from its body before experiencing its toxic action. This property, which is the result of an organism's individual mutation, is passed on to future generations, thus developing a poison–resistant population. In other words, the living body fights the external poisonous chemicals and prevents its destructive activity. This is natural selection in which individuals survive by adapting to changing environmental conditions.

Unlike all pesticide and other pest–control approaches, pheromones are essential ingredients for animals, in general, and insects in particular. Most important of all is the sex pheromone, without which there is no sexual mating between the mates, no fertilization and no next generation. Therefore, no resistance to the pheromone can develop. The reaction would probably consist of evading the impossibility of chemical communication by interfering with communication – mating disruption ("confusion"). In other words, by "confusion" we will cause the insects to try to "call" the other mate, but "look for" mechanisms to overcome the communication problem.

I propose to call this process evasion (rather than resistance), because there is no resistance here in the conventional sense of the word, as described above, so the different processes must be distinguished.

Q: What does this mean in terms of chemistry and biology?
A: We know that pheromones are usually a mixture of chemicals and the amount produced by the female is in nanograms. That is, there are two noteworthy factors here – the quantity and the quality, that is, the amount of pheromone produced by the female and/or the relative composition of the pheromone components.

Q: Do you mean to say that females can affect quantity and quality?
A: In principle yes, although not consciously, of course. We know that there is no complete uniformity in the quantity and composition of the pheromone among all females of the same

species. Moreover, different populations of the same biological species, located in different regions of the world, have different compositions, yet are still capable of transmitting genetic properties and reproduction. This situation can be seen as the beginning of the emergence of new species – speciation – a gradual variation in the pheromone composition, which will eventually lead to the termination of chemical linkage between the mates in the different populations, hence the termination of fertilization and the transmission of genetic code. This is the result of geographical isolation, which is known as a major cause for the emergence of new species.

Q: What's the connection of these things to our topic?
A: The connection is close as we can see right away. Remember, the "confusion" method is based on atmospheric saturation (relative to the natural concentration, of course) in the pheromone, so that the uniformity of the pheromone concentration in the air prevents the males from locating the females. Because the amount of pheromone distributed into the air differs among the females, the few females that release a large amount of pheromone into the air have a better chance of being the focus of attraction for males. If those females manage to mate (and we know that there is a certain percentage of success despite the "confusion") the ability to produce more pheromone will pass on their hereditary daughters, and granddaughters and future generations. That is, the "confusion" will cause an increase in the amount of pheromone in the population, as a first step to the pressure we exert on the insect through the pheromone and interference in the chemical communication.

Q: Can this be proven?
A: One way is to check a field where the confusion method was applied and see what happens. Indeed, in cotton fields in the United States, after the "confusion" of the pink bollworm moth (Pectinophora gossypiella) that lasted for 4 years, a 25% increase in pheromone production in females was found. This period corresponds to about 8–10 generations of the moth. A second way is to perform a lab experiment, despite the great differences between lab and field conditions.

Q: And what did you find?
A: After 7–8 generations of "confusion" in the laboratory, the amount of pheromone in females of a confused population was doubled compared to a normal population used as a control. This is clear proof that the "confusion" resulted in a natural selection of those females producing a higher titer of pheromone, while all those poor in pheromone failed to attract males and did not produce offspring. This is an example of the indirect evasion phenomenon mentioned above. There is no resistance here in the common sense, but evasion of the new situation encountered by the confused population. This was the first lab experiment of its kind in the world that demonstrated the possibility of evasion of confusion in terms of quantity [2].

Q: And what about the pheromone composition?
A: Here is my working hypothesis. The composition of the pheromone in the population differs among females and, for simplicity, we will focus on the case where there are only two components of the pheromone, and the composition varies in the population. This is described schematically in Figure 2a. The composition applied in the field in confusion is the average composition of the population, and the males are affected and cannot locate the females that release the average composition (Figure 2b). Females with a pheromone composition significantly different from the average composition can still attract those males that respond to these compositions (Figure 2c). Of course, it could be that the average new composition will shift to one side or another without separation to two populations.

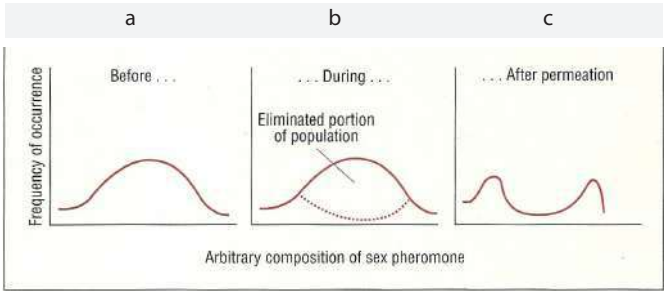


Figure 2. Schematic description of "confusion" in an insect population that produces a pheromone consisting of two pheromone components and a wide distribution of pheromone composition in the population. The possible result is the elimination of most of the population that responds to the average composition of pheromone applied to confusion and the development of marginalized populations, whose pheromone composition differs significantly from the original composition. Communication in these populations will be weakened considerably, resulting in two subspecies and then two new, though closely related, reproduction isolated species. This process is chemospeciation, which means speciation (appearance of new species) under the influence of chemicals.

Q: Sorry, if the composition is significantly different from the average composition, how do the males react?
A: Here it should be emphasized that there must be a match between the males and females regarding the chemical signal transmitted: if the composition is unmatched, chemical contact will stop and be damaged. Therefore, information regarding any change in the composition that the female produces and releases into the air must be transmitted to males (presumably this is done by way of inheritance from parents). In other words, just as females have a wide range of composition, so males have a wide range of sensors to

recognize and react to this composition. Therefore, only a few males will be able to locate these females, but this is enough to start a process of forming different populations. We see two minor populations present in the original population (Figure 2b). But since there is no vacuum in nature, the drastic reduction in the harmful population will allow these minor populations to develop and reproduce. These groups, as in the case of the geographic isolation I mentioned above, rarely "chat" between them, and their sexual attraction will weaken and disappear. The lack of a sexual encounter means no reproduction, and all that this implies, namely, the emergence of new species. This situation is shown in Figure 2c. I call this process chemospeciation, namely speciation under the influence of chemical factors. One point should be emphasized: The treated area should be large enough and, most important, isolated from other fields to eliminate any gravid females entering and adding more damaging larva and thus negatively affecting the mating disruption.

Q: Indeed, an interesting theory, involving work that is innovative. But is it true? Is there evidence of such a process?
A: In the experiments I performed above, while measuring the amount of pheromone produced by each female individually, I also tested the pheromone composition, but found no change in it. Also, in the field trial, with pink bollworm moth in cotton fields, which I mentioned earlier (25% increase in the amount of pheromone), no change was found in the composition.

Q: What does the composition mean?
A: It means the relative composition, that is, the ratio of pheromone components and this can vary. For example, in the case of two components, an average ratio of 3:1 could also be 2: 1 or 1: 1. If we look at data in Table 1, such differences do indeed appear to exist in nature between closely related species. The more complex process there will be removing or adding a new component to the pheromone. As mentioned above, only males who have inherited the composition information will be able to sense the new composition and locate the females distributing it.

Q: Is such a process possible?
A: From looking at the processes in nature we see that changes occur, and there is no doubt that the proposed process occurs by mutations and natural selection. It turns out that there are rare genes that can be expressed and cause "quantum jumps" in the traits. For example, in the case of a gene recently reported to be responsible for producing a pheromone composition different from the average composition established in the particular moth, this occurred by the addition of another isomer to the pheromone composition. This is an example of being in the same area, without geographical isolation, and is called sympatric speciation, a process whose existence in nature has been demonstrated many times, contrary to what was thought in the not too distant past.

Q: The basic biological meaning is clear, but what does it mean for pest control?
A: The result of the evasion process, whether by increasing the amount of pheromone distributed by the females or by a change in the composition, can immediately be traced. We can determine what is changing and act accordingly. If only the quantity is increasing, we can distribute a greater amount of pheromone in the field leading to more effective masking. To determine if the composition has changed, females can be collected from the field and their pheromone composition checked, either as an average or in individual cases, to see what changes have occurred. We can then immediately implement the new composition. Such a test can take several months to a year, resulting in an improved product that can fulfill its purpose in a short period of time. There is no need to synthesize thousands of new materials and test their effectiveness, on the one hand, and we will continue to keep reducing rates and their detrimental effect on animals and the environment, on the other. Thus, in the constant and incessant battle between humans and harmful insects, we will gain the upper hand, always one step ahead to prevent damage to agricultural crops and reduce ecological damage. So far, the "insect's hand" is on top.

Q: In conclusion, how do you apply these devices for interfering with the insect and "confusing" the insects in the field?
A: For over 30 years, since the pheromones began to be used for "confusion", all the devices are applied manually, whether it is a polyethylene lanyard containing the pheromone, which is released slowly through the cover, or vials, acting in the same manner, multi–layer polymeric preparations, and the like. Characteristic of all these is the need for much manpower during the short period of manual application. This is possible in a small plantation or field area, but not suitable for large areas of tens of thousands of acres or forests. What is needed is a product for the slow release of pheromones that can be sprayed from conventional spray equipment, whether tractor or airplane, and is active in the field for several weeks. So far, unfortunately, there is no such product on the market, mainly because of the high volatility of the pheromones released over a short time. Thus, the efficacy of the slow-release device is not sufficient to control insect pests in fruits and vegetables for human consumption. Cotton is now genetically modified and most cotton fields are planted with resistant plants with almost no damage caused by the main pests.

Q: What does this mean for the future?
A: The hope is that in the future, farmers and foresters will not use conventional pesticides at the outset, but will combine

agrotechnical methods with biological pest control methods using natural enemies and parasites, mating disruption with pheromones. They will only use pesticides as a last resort. In this way, resistance toward pesticides will be slowed down, the negative impact on the environment will be reduced, consumers will get products free (or almost free) of pesticides and the farmer can earn a living from his investment in producing the various types of agricultural products.

Q: Thanks for the detailed explanations.
A: Thank you for your interest and, if there are any further questions, I would be happy to answer.

New developments

Since retiring, I do not run active research, but follow the literature to see what other scientists do and learn from them. A short time ago, I found a paper [3] by authors from the Volcani Center, Israel, and Iowa State University. There I found what I had long been looking for – a report on mating disruption application with pheromones in the pink bollworm moth (*Pectinophora gossypiella*, Figure 3) and the appearance of a change in pheromone composition, as I forecasted years ago. The paper describes a change in the sex pheromone, which is a 1:1 mixture of two isomers (mentioned above in Table 1) to 62:38, which is not as effective as the natural one. One should notice that this happened after some thirty years of mating disruption of the pest in all cotton fields in Israel with no other cotton fields in the vicinity. As there are 4–5 generations per year, it means that at least 120 generations passed before the evasion took place.

Figure 3. Left: larva of the pink bollworm moth. Right, adult of the pink bollworm moth

My argument is that the "new" composition was already in the native population and it appeared after eliminating the majority of the native one. The claim that a change is in the genetics caused the change in composition seems unreasonable to me: why "create" something new, when it already exists in the population. The problem is that there is no population profile of the natural pheromone before the mating disruption mode started. Today there are no such insects in Israel. The only way to find out is to get native population from other fields, with the hope that the population there is really representative of the original population and pheromone composition. In any case, to tell the truth, I did not expect to see my hypothesis come true in my lifetime!

I wish you good reading. My articles dealing with pheromone collecting from live individual females are in Refs. [4–9].

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Vacuum technology in the extraction of cannabinoids

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Introduction

The use of the cannabis plant for the manufacturing of medicines is increasing enormously after its release as a remedy in many countries. Cannabinoids are of particular importance for medical applications. The primary active substances, cannabidiol (CBD) and tetrahydrocannabinol (THC), are mainly in demand from a medical perspective. Vacuum technology plays an important role in the industrial processing of cannabis to obtain high quality CBD and THC. It can be used for drying, extraction, evaporation and distillation. Vacuum technology alone enables the effective and efficient manufacturing of these pure active ingredients from the components of the cannabis plant.

Cannabis plants contain a variety of cannabinoids, terpenes, flavonoids and other substances. The psychoactive cannabinoid THC can be used for the treatment of allergies, pain therapy, anxiety and eating disorders and also in cancer therapy. The cannabinoid CBD promotes nervous system response and is analgesic and anti-inflammatory. CBD is also used in food and cosmetics. In addition to these two active ingredients, other products can be obtained from the hemp plant, such as saturated fatty acids, beta-carotene, omega-3 fatty acids and vitamin E.

The extraction of the active ingredients THC and CBD involves various processes (Figure 1). Some of them run under vacuum in order to enable the most effective and efficient manufacturing of these active ingredients. The various processes are described below.

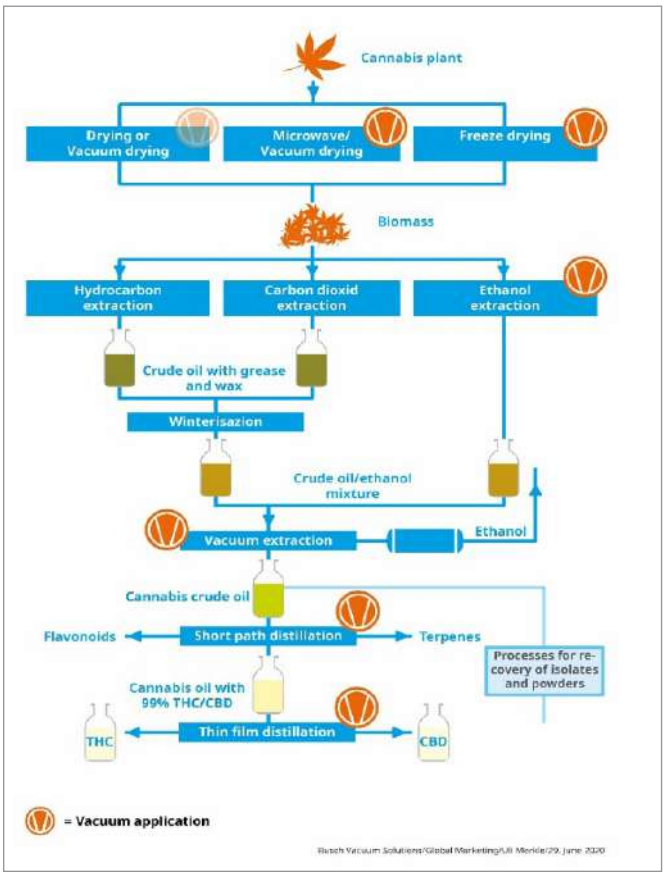

Figure 1. The process steps for obtaining CBD and THC. Source ©Busch Vacuum Solutions

Sammy Rabuchin was born in Copenhagen, Denmark and has lived in Kfar Saba since 1983. He is married with three children. He received his BSc in Mechanical Engineering from Ben-Gurion University of the Negev. He worked as a mechanical engineer at the Standards Institute of Israel and was then production and operation manager at Oxygen and Argon Works Ltd. He has fifteen years of experience as a vacuum sales and marketing engineer, previously at a vacuum representative company and currently at Busch Vacuum Israel Ltd.

Freeze drying

Freeze drying has become prevalent in the industrial drying of harvested cannabis plants. It enables fast, yet gentle drying of plants or plant parts that consist of 80% water. Freeze drying is based on the physical process of sublimation: Water passes under vacuum directly from a solid, frozen state to a gaseous state – the ice evaporates. The cannabis plants or their components are first deep-frozen at normal pressure. They are then subjected to a vacuum in which frozen water sublimates from the product, thus becoming gaseous. This allows the water to be suctioned off as vapor without heating it. This means that the substances are not negatively affected either by excessively high temperatures or by a long drying period. The correct use of vacuum technology is important for this drying process. Normally, depending on the plant, absolute pressures of 0.001 to 0.5 millibar are used for freeze drying.

Another drying method is microwave-assisted drying. This procedure is faster than freeze drying. The pressure level lies in the range 10 to 400 mbar.

Extraction

During extraction, cannabis oil is obtained from the dried plant parts – the so-called biomass. Cannabis oil is an extract from the cannabis plant that, unprocessed, contains a variety of cannabinoids. The most desired ones are CBD and THC, which account for between 60 and 80 percent. Furthermore, cannabis oil contains essential oils (terpenes), flavonoids, lipids, waxes and grease. The composition of this raw oil depends on the plant itself or on the components used, the extraction method chosen and parameters such as temperature, pressure conditions and extraction time.

Hydrocarbon and carbon dioxide extraction were initially the most common methods of extracting oil from the cannabis plant. Both extraction processes require subsequent winterization in which the crude oil is mixed with ethanol, cooled to -40 °C and subjected to cold filtration. This removes waxes and grease from the oil.

Ethanol extraction

Ethanol extraction has become established in the industrial processing of the cannabis plant. This procedure combines the high efficiency of hydrocarbon extraction with the high level of safety of carbon-dioxide extraction. There is also no need for winterization. Since ethanol is a very effective solvent that also extracts undesirable substances from the biomass, extraction is carried out with supercooled (cryogenic) ethanol under vacuum at absolute pressures of 0.001 to 1 mbar (Figure 2). The desired extraction properties are thus achieved. The intermediate product of the extraction is always a mixture of cannabis oil and ethanol.

Figure 2. Two-stage rotary-vane vacuum pumps and scroll vacuum pumps often used for freeze drying, ethanol extraction, short-path and thin-film distillation in laboratories and for processing smaller quantities. Source ©Busch Vacuum Solutions

Vacuum evaporation

The cannabis oil/ethanol mixture is then fed into an evaporation process to remove the ethanol it contains. Due to ethanol's low boiling point, this can be done in lab or pilot-scale processes in a rotary evaporator at room temperature or with modest heat addition and a vacuum of 50 to 100 mbar. Liquid-ring vacuum pumps with ethanol as operating fluid can be used for this. The ethanol can be re-liquefied via a condenser and fed into the cycle.

For industrial-scale operation, thin or wipe film evaporators can be used to efficiently remove the bulk of the solvent producing the crude oil, working at a higher vacuum level. After vacuum evaporation, crude oil with a THC/CBD concentration of 60 to 80 percent is obtained.

Distillation

As well as cannabinoids, the cannabis crude oil contains terpenes as aromatic oils and flavonoids as bioactive flavor carriers. They need to be separated in a distillation process. One of the most commonly used and most efficient distillation processes is the so-called short-path distillation. This involves taking the different boiling points of the individual components of the oil under certain temperatures and pressures into account for the separation. While THC begins to evaporate at an atmospheric pressure of 157 °C, CBD evaporates at 160 to 180 °C. Individual terpenes and flavonoids have lower boiling points. Carrying out the distillation under

vacuum allows for a reduction in the temperatures required to boil the various cannabinoids. Short-path distillation works at a vacuum level of 0.001 to 1 mbar (Figure 3). The oil is slowly heated and the vacuum level adjusted so that terpenes and flavonoids evaporate selectively and can be obtained by condensation. What remains as concentrate is a liquid containing the cannabinoids THC and CBD in 99% purity.

Figure 3. Vacuum systems with screw vacuum pumps and vacuum boosters ideally suited to many industrial cannabinoid extraction processes. Source ©Busch Vacuum Solutions

In a second distillation step, the THC is separated from the CBD in a thin-film evaporator. Thin-film evaporators operate similarly to short-path distillators under vacuum and different temperatures. In principle, distillation is carried out at vacuum levels of around 1 mbar and higher temperatures. To activate the psychoactive effect of THC, this cannabinoid must be heated to 104 °C – a process called decarboxylation. If this temperature is not reached during distillation, decarboxylation must be carried out in an intermediate step before distillation. In this last process step, pure CBD and THC are finally obtained, which can now be further processed as active ingredients for various applications.

Conclusion

The methods used to obtain CBD and THC vary, and depend on the type of cannabis and the amount processed. Therefore, the vacuum technology used, the technical parameters of the vacuum pump, such as the ultimate achievable pressure or its pumping speed, must also be individually adapted to the specific processes. A combination of vacuum pumps can also make both economic and technical sense, for example to accelerate processes or to protect heat-sensitive materials from excessive temperatures. It is therefore essential to consult a vacuum specialist when selecting the vacuum supply. A number of companies offer a wide range of vacuum pumps and individual vacuum systems for all applications, together with personal and comprehensive advice. Table 1 gives an indication of the vacuum technologies that can be used.

Table 1. Possible vacuum technologies for use in the various processes. Source ©Busch Vacuum Solutions

Application		Vacuum range	Vacuum technology	
			Laboratory/Small quantities	Industrial production
DRYING	Freeze drying	0,001 - 0,5 mbar	Scroll Two-stage rotary vane	Screw Screw with vacuum booster
	Microwave/ vacuum drying	10 - 400 mbar	Single-stage rotary vane Rotary claw	Single-stage rotary vane Rotary claw
EXTRACTION	Ethanol extraction	0,001 - 1 mbar	Scroll Two-stage rotary vane	Srew Screw with vacuum booster
EVAVORATION	Rotation evaporator	50 - 100 mbar	Liquid ring Single-stage rotary vane	Liquid ring Single-stage rotary vane
	Thin film evaporator	1 mbar	-	Screw Screw with vacuum booster
DISTILLATION	Short path evaporator	0,001 - 1 mbar	Scroll Two-stage rotary vane Two-stage rotary vane with turbomolecular	Screw Screw with vacuum booster
	Thin film evaporator	1 mbar	Scroll Two-stage rotary vane	Screw Screw with vacuum booster

Baruch Blumberg (1925-2011) and the discovery of the Hepatitis B virus, diagnostic methods for detection, and vaccine

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Abstract

Baruch Blumberg's research was designed to gain a better understanding of the role of human genetic polymorphisms in relation to inherited susceptibility to disease. This led to the discovery of the hepatitis B virus, diagnostic methods for viral detection and a vaccine. The vaccination program has prevented the death of millions from primary liver cancer. It was the first widely used vaccine against cancer. For his work with the hepatitis B virus, Blumberg was honored in 1976 by the award of the Nobel Prize in Medicine or Physiology.

Introduction

Baruch Blumberg's (1925-2011) research was initially designed to gain a better understanding of the role of human genetic polymorphisms in relation to inherited susceptibility to disease. Blumberg: "At the onset, there was no obvious practical application of this project. However, building on a large body of research on hepatitis over the preceding decades, these studies resulted in the discovery of the hepatitis B virus (HBV), diagnostic methods for viral detection, and a vaccine. These applications have had a major impact on worldwide medical and public health problems…Hepatitis B vaccination is one of the largest worldwide disease-prevention programs. It has decreased the spread of HBV, particularly in China and East Asia. It has significantly decreased morbidity from liver disease and prevented the death of millions. HBV vaccination appears to prevent primary cancer of the liver; it is the first widely used preventative cancer vaccine." For his work with HBV, Dr. Blumberg was honored in 1976 by the award of the Nobel Prize in Medicine or Physiology. Blumberg had an association with Ben-Gurion University of the Negev for several years, see Figures 1 and 2 [1, 2].

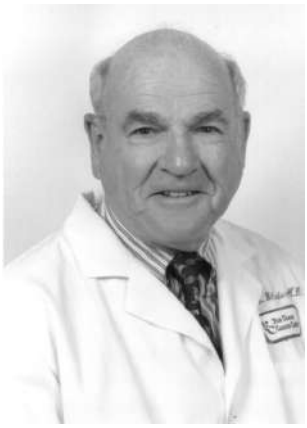

Figure 1. Baruch Blumberg. Photograph courtesy of B. Blumberg.

Bob Weintraub was born in Brooklyn, New York and made aliyah in 1975 to Beer Sheva, where he remained. He earned the PhD in Physical Chemistry from MIT and the Diploma in Library Science from the Hebrew University of Jerusalem. He held positions in scientific and technical librarianship in industry, hospital and academic institutions. He is now retired. He has an interest in the history of chemistry.

Figure 2. Baruch Blumberg delivering the Zlotowski Annual Lecture at the Ben-Gurion University of the Negev on May 9, 2010, entitled, "Strategies of Human Disease Control-The Hepatitis B Programs." In the lecture, attended by the author, Dr. Blumberg showed that the hepatitis-B vaccine program up until that time had prevented an estimated 29 million deaths from liver cancer. Photograph courtesy of Dani Machlis/Ben-Gurion University of the Negev.

Baruch Blumberg

Baruch S. Blumberg was born in Brooklyn, New York, in 1925, into a Jewish family. He earned his undergraduate degree in physics at Union College in New York State. Following war service in the Navy, he earned his medical degree in 1951 from the Columbia University College of Physicians and Surgeons. In 1957, he earned his DPhil from Oxford University in biochemistry for his work on hyaluronic acid. Blumberg accepted a position at the National Institutes of Health in Bethesda, Maryland and in 1964 moved to the Institute for Cancer Research in Philadelphia, now called the Fox Chase Cancer Center. He remained there except for extended periods away in England, California, and elsewhere [1–4].

Genetic polymorphism

Genetic polymorphism (inherited biochemical and immunologic variation in human populations) is a concept introduced by the lepidopterist and professor of ecological genetics E. B. Ford of the Department of Zoology at Oxford. He defined it as the occurrence together in the same habitat of two or more (inherited) discontinuous forms of a species in such proportions that the rarest of them cannot be maintained merely by recurrent mutation. Blumberg, in recalling his time at Oxford: "It began to dawn on me that the study of human polymorphisms would provide a conceptual framework for the investigation of inherited human variation and its connections with disease and survival, and that the gel method of electrophoresis could be a main technique for identifying the variation…Our grand plan was to track the distribution of the polymorphic traits in populations living under very different environmental conditions, where the health risks would vary greatly. We expected that different disease risks would have generated different selection pressures, and that the frequency of the genes determining the polymorphisms would vary. Also, we would be more likely to find previously undiscovered associations between disease and polymorphisms…It was during the course of our study of human polymorphisms that we, unexpectedly, discovered the hepatitis B virus." [3]

Blumberg: "The blood cell antigens were an example of inherited differences in susceptibility to disease. If an individual had inherited a particular combination of antigens, he or she would be susceptible to transfusion reactions if transfused with blood containing different antigens; if transfused with the same antigens, the person was protected against a transfusion reaction. The ABO red blood cell antigens were among the first of the systems of inherited common biochemical traits, called polymorphisms, studied by scientists…

The original concept of polymorphism implied that there are survival benefits conferred by some combinations of alleles that other combinations do not provide, and that there is heterozygote advantage. However, it has been difficult to demonstrate advantage for many polymorphic traits. It is possible that polymorphisms are selectively neutral and occur as a consequence of chance. In many instances the selective advantage of a single polymorphic system taken by itself may be too small to detect. But if a given polymorphism is considered along with other polymorphic traits and with environmental factors with which they could interact, selective advantage may be detected.

Independent of the question of selection, the polymorphic systems provided an excellent mechanism for studying biochemical and immunologic variation among individuals and among human populations." [3]

Hepatitis B Virus

In 1963, Blumberg and his colleagues observed a reaction between an antigen from sera of an Australian with an antibody from sera of a New York hemophilia patient. The sera of hemophilia patients who have received many transfusions was often used in experiments as they are exposed to sera from many donors and are likely to become infected with blood-borne agents or to develop antibodies against serum proteins.

"I'm often asked why we were testing sera from Australian aborigines. The answer derives from our overriding interest in human inherited variation—polymorphisms. Our long-term goal in studying what at that time was an esoteric field in human population genetics was to find relations between these polymorphisms and differences in susceptibility to disease. We knew that the frequency of polymorphic alleles varies greatly from population to population and from country to country. In looking for a new polymorphism without any knowledge of the population distribution of the alleles, we reckoned that we could increase the probability of success by randomizing the populations used in the screens of the transfused sera from different populations, and the screen in which the new antiserum was found included, not exactly by chance, Australian aborigines. " [3]

The serum of the hemophiliac was then tested against thousands of serum samples. Observations started to point to the hypothesis that the Australia antigen (later known as the hepatitis B surface antigen, designated as HBsAg) was a part of the hepatitis virus. The antigen was being observed in many samples from patients with hepatitis, among other indications. Tom London and Irving Millman made the important observation that when the highly purified fraction of the Australia antigen was used in injection experiments with vervet monkeys the infection did not occur, but if less purified material was used, the vervet became infected. This lead to the understanding that the purification process separated the infectious particle (still unobserved) that could cause the disease from the noninfectious particles (that were observed in the electron microscope). Blumberg: "Oddly, most of the important applications of the research on HBV were realized before there was a significant understanding of the virus's molecular details." [3]

Hospital post-transfusion hepatitis used to be a major complication of surgery. By 1967, a test was devised for the presence of the Australia antigen which indicated the presence of hepatitis B in occult carriers and also could be used to diagnose patients with hepatitis B. By the mid 1970's, post-transfusion HBV had virtually disappeared in countries where compulsory testing had been instituted. Later, in the 1980's, hepatitis C virus was discovered and a method of testing for it was worked out. Other hepatitis viruses have since been discovered, D, E, and G, but they present a much lesser clinical problem than that of the B and C viruses. It has been estimated that the annual saving resulting from the prevention of post-transfusion hepatitis amounts to about half a billion dollars in the United States.

Invention of the vaccine

Blumberg: "In 1968 we were informed by the Federal government, who provided most of the funds for our work, that they would like to see applications of the basic research they had funded for many years. It occurred to us that the existence of the carrier state provided an unusual method for the production of a vaccine. We presumed that the very large amounts of HBsAg present in the blood could be separated from any infectious particles and used as an antigen for eliciting the production of antibodies. The antibodies in turn would protect against infection with the virus. Irving Millman and I applied separation techniques for isolating and purifying the surface antigen and proposed using this material as a vaccine. To our knowledge, this was a unique approach to the production of a vaccine; that is, obtaining the immunizing antigen directly from the blood of human carriers of the virus. In October, 1969, acting on behalf of ICR [Institute for Cancer Research] we filed an application for a patent for the production of a vaccine. This patent [USP 3,636,191] was subsequently (January, 1972) granted in the United States and other countries." [4]

Primary hepatocellular carcinoma

HBV is transmitted by transfusion, sexually, from mother to child at birth, and by contaminated needles. The association of chronic liver disease with cancer of the liver had been recognized since the 1950's, but it took the identification of the HBV to enable the interconnection to be made between HBV, cancer of the liver, and chronic liver disease. Blumberg's group first proposed this connection in 1969, two years after their first publication on HBV. "Primary hepatocellular carcinoma (HCC) is a cancer that originates in the liver. The cancer process may start in the liver cells for a susceptible person at a very young age; the affected cells initially divide and reproduce themselves very slowly…The slow growth proceeds over many decades, unknown to the host and without any symptoms." HCC usually occurs in people who already have liver disease, typically due to HBV or HCV. When symptoms finally do appear, often several decades after HBV infection, the patient generally dies within 6-20 months. The five-year relative survival rate is 18 percent." [4–6]

Manufacture of the Vaccine

Blumberg: "It took some time before the concept was accepted by virologists and vaccine manufacturers who were more accustomed to dealing with vaccines produced by attenuation of viruses, or the use of killed viruses produced in tissue culture, or related viruses that were non-pathogenic but

protective (i.e., smallpox). However, by 1971, we were able to interest Merck, which had considerable experience with vaccines. During the next few years, a series of human and primate observations by scientists including [M.] Hilleman (who was responsible for vaccines at Merck), S. Krugman, R. Purcell, P. Maupas, and others provided additional support for the vaccine. In 1980, the results of the first field trial were published by W. Szmuness and his colleagues in New York City. They showed that the vaccine was highly effective (over 90% were protected) and that no untoward side effects were observed. The FDA approvals were obtained, and by 1982 the vaccine was available for general use." [2] Soon afterwards, recombinant HBsAg vaccine was developed in several laboratories. HBV vaccine was the first vaccine to be produced commercially by recombinant methods. Within a few years of the approval of the vaccine, millions of children and adults were being vaccinated yearly. The vaccine is one of the most commonly used vaccines in the world. It is a compulsory vaccination for a large percentage of the world's population.

In 2002, Blumberg reviewed the grim worldwide statistics of death and liver cancer brought on by HBV infection. At that time, about 1.5 million people were dying each year as a consequence of HBV infection. He wrote: "The presentation of such grim figures as these usually precede a prediction of even more awful events. But that is not the case for HBV. Life – and death – are full of surprises, and while it may be tempting fate to be too optimistic, it appears likely that within the next few decades the virus will be effectively controlled. It is even possible that it will be eradicated." [3]

Israel

Blumberg had an association with Ben-Gurion University of Negev for several years and wrote to the author that he has been gratified to see it grow and continue its valuable research in medicine and the science of arid environments. He recalled that on his first visit to Israel in 1953 he visited Hadassah medical system hospitals in Jerusalem, Safad, Beersheva, and elsewhere. He visited these sites and other sites several times after and commented that he had never been anywhere that has changed as much as Israel.

Blumberg recalled attending meetings with the late Dr. Chaim Sheba and, in March 1973, a memorial symposium in honor of Dr. Sheba on polymorphisms, population biology, and inherited susceptibility to disease. He began his presentation at that meeting with an explanation of the significance of a finding by Dr. Batsheva Bonné (later, Prof. Bonné-Tamir, Human Molecular Genetics & Biochemistry, Tel-Aviv University), who came to his laboratory with a collection of sera from the Samaritan population of Israel. She found the presence of the Australia antigen in the sera of two sibs, products of a consanguineous marriage, of the 125 persons tested. Bonné-Tamir in 1994 established (together with Mia Horwitz) the National Laboratory for the Genetics of Israeli Populations [7–9].

If you save a single life, you save the whole world

Blumberg saw saving lives as the whole point of his career. "It was something that I always wanted to do and is what drew me to medicine. There is, in Jewish thought, this idea that if you save a single life, you save the whole world, and that affected me." [10]

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Creating Much Out of Nothing: The Relationship between Fritz Haber and Chaim Weizmann

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Abstract

In the early 1930s, as Nazism was gaining strength in Germany, two renowned German-speaking Jewish scientists found themselves on converging paths: Fritz Haber (1868–1934), one of the most influential and controversial of 20th century chemists and Chaim Weizmann (1874–1952), a successful biochemist, leader of the world Zionist movement, and future founder of the State of Israel. In their meetings and correspondence, they reflect on the history, current events, and fate of science and scientists, and strive to create a place where learning and humanism would rise above racism and hatred. This article is adapted from a recently published full-length paper [Bielik and Friedrich, *Israel Journal of Chemistry*, 2020, **60**, 1061 – 1076.

1. Prologue

The first apparent contact between Fritz Haber and Chaim Weizmann, dating back to March 1921, was indirect but consequential. As noted in Weizmann's autobiography [1, p. 352]:

> It will be remembered that when I made my first trip to America, in 1921, I had been fortunate enough to enlist the co-operation of [Albert] Einstein. I learned later that Haber had done all he could to dissuade Einstein from joining me; he said, among other things, that Einstein would be doing untold harm to his career and to the name of the institute of which he was a distinguished member if he threw in his lot with the Zionists, and particularly with such pronounced Zionists as myself.

It would take nearly twelve years and the mediation of Weizmann's brother-in-law, Josef Blumenfeld (1901–1981), as well as Haber's son, Hermann Haber (1902–1946), for the two men to close the distance between them and to meet face to face. When they finally did, in London, Weizmann quickly warmed up to Haber: "I found [Haber], somewhat to my surprise, extremely affable" [1, p. 352]. From then on, a rather congenial relationship developed between Haber and Weizmann that hinged on Weizmann's Zionist project of building academic institutions in British Mandate Palestine and Haber's outstanding ability to help its advancement. In what follows, we follow the timeline of their mutual encounters – and of Haber's changing attitudes in response to the rise of Nazism – that nearly culminated in Haber's resettling to Palestine. Our principal guide will be their mutual correspondence (29 letters retrieved from the Weizmann Archives in Rehovot), as well as correspondence

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with others. Had Haber's ill health – and death – not cut short his journey to join Weizmann in Mandatory Palestine, Israeli science could have benefited not only from the involvement of Haber's pupils and colleagues, but also from the leadership of Haber himself.

Figure 1. Zionist delegation to the U.S., 2 April 1921. From left to right: Menachem Ussishkin (head of the Zionist Commission and later President of the Jewish National Fund), Chaim Weizmann, Vera Weizmann, Albert Einstein, Else Einstein, and Ben-Zion Mossenson (Member of the Jewish National Council). Wiki Commons.

However, before setting out on a tour along the timeline of their mutual encounters, let us quote what Haber had actually written to his friend Einstein in connection with Einstein's planned trip to the UK and USA as a member of a Zionist delegation [2]:

> It is the friendship of many years that forces me to write to you today. … If at this point in time you ostentatiously fraternize with the English and their friends, the people [in Germany] will regard it as a proof of the disloyalty of the Jews. So many Jews went into the war [WWI], died, and ended up in misery, without complaining about it, because they saw their service as a [patriotic] duty. Their lives and deaths have not eliminated anti-Semitism, but have relegated it, in the eyes of those who shoulder the honor and greatness of our country, to [the category of] base hatefulness and ignobility. Do you wish to erase through your behavior what German Jews have achieved with their blood and suffering?

In America, Einstein was treated as a celebrity (Figure 1) [3]. Back in Berlin, Einstein's success abroad was regarded as homage paid to a *German* scientist – and no incidents related to Einstein's trip are on record. However, serious incidents followed not long thereafter, as the anti-Semitic (and anti-socialist) conspiracy theory of a "stab in the back" was taking hold in Germany [4].

2. Timeline of personal meetings between Fritz Haber and Chaim Weizmann

First meeting (London, 1932)

As noted above, Haber and Weizmann were introduced to each other in person as late as 1932 – by their family members (the exact date of the meeting is unknown) [5, p. 361]. At their amicable meeting in London, Haber was still the omnipotent German *Geheimrat* (privy councilor) while Weizmann, a British subject, was the leader of the Zionist movement. A year earlier, Weizmann was voted out of office as president of the World Zionist Organization. Disappointed by the disapproval of his liberal political leadership, Weizmann concentrated on establishing a new biochemistry research institute in the town of Rehovot in Palestine, with the support of the British Zionist sympathizers, Israel and Rebecca Sieff [1]. This was far from a mere distraction for Weizmann. As Fritz Stern put it [6, p. 231]:

> For most liberals at the time, science was an unquestioned good, the fullest expression of human reason and human genius, an obvious instrument of human progress.

At their London meeting, Weizmann outlined his project in Rehovot to Haber, whereupon Haber "invited [Weizmann] to visit him at his research institute [in Berlin]" [1, p. 352].

Figure 2. Fritz Haber with Richard Willstätter, in Kloster, Switzerland, in 1929. Archiv der Max-Planck-Gesellschaft.

Second meeting (Berlin, 5 December 1932)

Weizmann accepted Haber's invitation and visited him at his Kaiser Wilhelm Institute (KWI) for Physical Chemistry and Electrochemistry in Berlin-Dahlem on 5 December 1932 [7], less than two months before Adolf Hitler's rise to power in Germany. Here is how Weizmann described his visit [1, p. 352]:

> It was a magnificent collection of laboratories, superbly equipped, and many sided in its program, and Haber was enthroned as dictator … He was not only hospitable; he was actually interested in my work in Palestine. Frequently in our conversation on technical matters, he would throw in the words: "Well, Dr. Weizmann, you might try to introduce that in Palestine."

In fact, Weizmann was impressed by what he saw in Dahlem to the extent that he decided to model what was to become the Daniel Sieff Research Institute on Haber's KWI. The impending political catastrophe in Germany is alluded to in a letter that Haber sent to Weizmann on 21 May 1933 from Munich, where he was visiting his bosom friend Richard Willstätter (1872–1942), see Figure 2. Although Haber did not explicitly mention his own predicament under the Nazi rule, he noted that Willstätter was reluctant to even consider moving out of Munich.

And a predicament it was: Soon after the promulgation of the "Law for the Restoration of the Professional Civil Service" – designed to exclude Jews and political opponents from civil service positions in Nazi Germany – on 7 April 1933, Haber found himself under the obligation to dismiss twelve of his coworkers of Jewish descent from the KWI (out of forty nine) [8, p. 651]. Under a threat from the Ministry of Science, Education, and Culture that the Society would come under a Nazi commissioner should the law not be enforced immediately and concurrent pressure from the Kaiser Wilhelm Society, Haber dismissed, on 29 April 1933, his assistants Ladislaus Farkas (1904–1948) and Leopold Frommer (1894–1943) [8, p. 656]. The law did not apply to Haber himself, as there was a clause that exempted the veterans of World War One who served on the front. The next day, Haber resigned from all his positions in protest against the law. Haber submitted his memorable letter of resignation on 30 April 1933 to the infamous *Kultusminister* Bernhard Rust, in which he noted [9]:

> My sense of tradition requires of me that… I only choose staff members according to their professional abilities and character, without regard to their racial make-up.

The resignation was to take effect on 30 September 1933, the day the law entered into force.

Third meeting (Paris, 10 August 1933)

Haber left Berlin on 5 August 1933 – unaware that he would never return. His first destination was Santander in Spain, where the officials of the International Union of Pure and Applied Chemistry (IUPAC) were to hold a preparatory meeting on August 9–20, 1933 for the forthcoming 1934 IUPAC Congress [10]. Joined on the trip by Richard Willstätter, Haber made a stopover in Paris to see Weizmann again. They met on 10 August, in the presence of Willstätter and Weizmann's assistant, Ernst David Bergmann [11]. This was a key moment in Haber's new life in exile, as Weizmann laid out his detailed plans for the Sieff Institute and offered both Haber and Willstätter leading positions there.

In his autobiography, Weizmann recollects the circumstances and the way he extended his invitation to Haber [1, p. 352]:

> [I] found [Haber] broken, muddled, moving about in a mental and moral vacuum. … The shock had been too great. He had occupied too high a position in Germany; his fall was therefore all the harder to bear. … I began to talk to him then about coming out to us in Palestine, but did not press the matter. I wanted him first to take a rest, recover from his shock and treat his illness [angina pectoris] in a suitable climate.

In addition, Weizmann offered Haber to make use of his connections at the British Foreign Office to help Haber to get out of Germany without having to pay the emigration tax [Reichsfluchtsteuer] [8, p. 688], [12]. Haber understood Weizmann as suggesting that, in the coming years, he would spend regularly the winter terms in Palestine, helping Weizmann with setting up the Sieff Institute. But before committing, Haber wanted to see the place and the people and offered to visit Rehovot at the beginning of 1934.

Following his visit to Spain, Haber returned to a sanitarium [Kurhaus] in Switzerland. Shortly thereafter, he learned that Weizmann was vacationing nearby, in Zermatt, Switzerland. Haber decided to pay him a visit, ignoring the warnings of his doctors, including Rudolf Stern's, that he should avoid high altitudes because of his heart condition (Zermatt is located at the foot of the Matterhorn, at about 1600 m).

Fourth meeting (Zermatt, 25 August 1933)

At and after the meeting in Zermatt, the plan for Haber's involvement in Weizmann's project in Palestine started taking concrete shape [1, p. 357; 13]. Haber's high altitude visit with the Weizmanns was happening against the background of the 18th Congress of the World Zionist Organization that

was taking place in Prague from 21 August until 4 September 1933. As Weizmann explains in his memoirs, he did not intend to attend the Congress, despite the importance for Jews to speak in one voice during the crisis brought about by the rise of the Nazis to power in Germany [1, pp. 353-354]:

> I had refused to attend [the Congress], not wishing to be involved in any political struggle. During the dinner [with Haber, Weizmann's wife Vera and their son Michael] repeated [phone] calls came from Prague, and frantic requests that I leave Zermatt at once and betake myself to the Congress. I persisted in my refusal, and though I said nothing to Haber about [the reason for] these frequent interruptions, except to mention that they came from Prague, he guessed their purport from something he read in the papers, and he said to me, with the utmost earnestness: Dr. Weizmann, I was one of the mightiest men in Germany. I was more than a great army commander, more than a captain of industry. I was the founder of industries; my work was essential for the economic and military expansion of Germany. All doors were open to me. But the position which I occupied then, glamorous as it may have seemed, is as nothing compared with yours. You are not creating out of plenty – you are creating *out of nothing* [our emphasis] , in a land which lacks everything; you are trying to restore a derelict people to a sense of dignity. And you are, I think, succeeding. At the end of my life I find myself a bankrupt. When I am gone and forgotten your work will stand, a shining monument, in the long history of our people. Do not ignore the call now; go to Prague, even at the risk that you will suffer grievous disappointment there.

Haber's speech in Zermatt is often quoted, but seldom with the point about the significance that he attributed to Weizmann's work. Weizmann "did not go to Prague, much to Haber's disappointment," but he [1, p. 354]:

> took the opportunity to press upon [Haber] our invitation to come out to Palestine and work with us. I said: "The climate will be good for you. You will find a modern laboratory and able assistants. You will work in peace and honor. It will be a return home for you – your journey's end." He accepted with enthusiasm and asked only that he be allowed to spend another month or two in a sanitarium.

What happened next is captured in Rudolf Stern's recollections [14, p. 100]:

> On leaving Zermatt, Haber suffered a complete breakdown in the little town of Brig; he himself thought it was an apoplectic fit while, from his later descriptions, I was more inclined to consider it a heart failure. Anyhow, he recovered sufficiently to be able to travel to the Swiss sanitarium in Mammern where he spent the whole of September [and October] under competent medical care and in the company of his always helpful and understanding stepsister, Else Freyhan.

Still from Brig, Haber reported about his state to Weizmann [15]:

> I'm again in full possession of my body, speech, and mental capacity and have only thoroughly spoilt the summer holiday car trip for my son Hermann and his French friends. No more will I ride up to the elevation of 1600 meters and then down from there again, but I am glad that my last mountain trip has given me the opportunity to meet you and your wife and Mrs. Hadassah Samuel as well as to see, for the first time in my life, the Matterhorn, which occupies a very special place among mountains, as you do among men. … I kindly request your permission to stay in touch with you with regard to Palestine and to the eventual help that I may need in order to be able to extricate myself from Germany. I would be most grateful if you could write me a letter inviting me to spend a part of the year in England and the rest in Palestine, should the English climate be too rough for me. I could then use this letter with the lower authorities in Germany in the case the higher authorities make no trouble for me when I will be leaving the country, without the need to involve the Foreign Office. … I have two fully furnished houses [directorial mansion in Dahlem and a farmhouse in Witzmanns near Bodensee] and the furnishings will have to go either to France [apparently to Hermann Haber] or to Palestine.

From Mammern, Haber continued exchanging letters with Weizmann about plans for Palestine while Weizmann was implementing these plans on the Palestine side, as attested to by his correspondence with Haber and with his colleagues in Rehovot. The plans included setting up Haber's laboratory and finding suitable accommodation for him [16, 17]. Weizmann was able to report to Haber on the progress achieved [18]:

> I am happy to inform you that the outer shell of the building is ready, and the people there are beginning with the inner outfit. … I am assured that the laboratory will be in working order on January 1st, so that if we all get there during December, we shall find a great deal to do. I have instructed Palestine to look for accommodation … and would be glad to know approximately what accommodation you will require. Who will be travelling with you? Of course, at the beginning accommodation will be rather scanty, and perhaps Spartan, but we shall soon have comfortable quarters for you. Will you be taking

> some of your Library with you? And will your sister and your secretary be accompanying you?

Haber replied [17]:

> In any case, my situation requires further consideration, before I can make a final decision about whether to undertake such a long trip … For such a trip I would need the company of my sister, Ms. [Else] Freyhan, as my health situation is uncertain … I have considerably recovered since my breakdown [in Brig] … but I don't think I can take upon myself to travel to the Near-East on my own. I intend to stay here until mid-October … and then to travel to Orsellina [in the Locarno area of Switzerland] and stay there for a while, and from there continue by ship from Genoa either to Alexandria and from there to Cairo and Jerusalem to visit you and your wife; or should a suitable ship be available, sail directly from Genoa to Haifa.

Haber further ventures to recommend Ladislaus Farkas as his most suitable assistant – and potential successor should Haber assume the chair of physical chemistry at The Hebrew University of Jerusalem – and suggests to Weizmann to invite Farkas for a visit in London (Farkas was just about to start a fellowship in Cambridge). In the letter, Haber goes on to describe his disappointment about the outcome of the 18th Zionist Congress that did not result in re-electing Weizmann as WZO's President:

> I certainly understand that under the [adverse] circumstances in Prague you could not have accepted the presidency. However, I was highly disappointed that the Congress participants could not, in light of the present situation, set aside their differences and unite in voting for you. They are lucky that the National Socialists in Germany give them more time – in that that they are not softening their position toward people of different views than theirs, but rather sharpening [their position] to the extent that my colleagues of purely Aryan descent are beginning to see the situation as unbearable and have started looking for new jobs in foreign countries.

Finally, Haber vents his views on what the rise of Nazism in Germany means for German and European chemistry and chemical industry and outlines his vision of the opportunity the decline on the European continent may open for Palestine and Turkey:

> German chemistry dislodged, in about 1870, English chemistry from the leadership position, whereupon French chemistry, which in the time of Liebig had a great weight, dropped out as well. Now, I assume, the German position is up for grabs and the question is who will take it. … The continuation of a great project with the help of people who were chosen in the first place according to their political views seems hopeless to me in Germany. And even if Palestine is not strong enough to take the place of Germany, your reorganization of the University of Jerusalem and the ongoing restructuring of the University of Istanbul will ignite a light in the east that has all it takes to become a bright light for the whole world.

At the beginning of November, refreshed by his sojourn in Mammern, Haber, accompanied by his stepsister Else, set out for Cambridge. They reached their destination, after stopovers in Paris and London, on 7 November. Weizmann did his best to support Haber during the time in Cambridge. Upon Haber's arrival there, Weizmann wrote the following [19]:

> I somehow feel that you are perhaps a little bit uneasy during these first few days at Cambridge, and I would like you to know how much I understand and sympathize with you; the first few days in strange surroundings are always difficult. But I am sure that that feeling will pass very soon, and that you will shortly be finding the atmosphere a congenial and friendly one in which you can carry on your work under really happy conditions.

During his nearly three-month stay in Cambridge, Haber had been visited by many of his former coworkers and colleagues, among them Michael Polanyi (1891–1976), Paul Harteck (1902–1985), Ladislaus Farkas, and Max Born (1882–1970). A happy moment was a colloquium given by Haber's Dahlem coworkers in his room at the University Arms Hotel. As Haber's former "chief of staff," Hartmut Kallmann (1896–1978), recollected "a scientific discussion [unfolded] more wonderful than you can imagine" [5, pp.610-611]. In addition to all the activities reflected in his correspondence, Haber worked hard on his science in Cambridge: he wrote there his last paper, on catalytic decomposition of hydrogen peroxide [20], a paragon of thoroughness and ingenuity, nineteen printed pages long. According to Haber's stepsister Else, it cost him the "last ounce of his strength" [5, p. 612]. The co-author was Haber's Berlin assistant Josef J. Weiss (1905–1972). It was also in Cambridge where Haber would give his last lecture, on 23 January 1934 [8, p.691]. For his 65th birthday on 9 December 1933, Haber received a great number of congratulatory letters, among them one from Carl Bosch (1874–1940), then Chairman of the Board of IG-Farben.

In his key letter to Weizmann [21], Haber made clear, on the one hand, that he would not be able to come to Palestine in the near future, and, on the other, that he had embraced the Zionist cause. As for the former, Haber informed Weizmann about the lack of progress concerning his emigration from Germany: the visit by the British Ambassador at the

German ministries in Berlin "on whose effect [Haber] built a skyscraper" was to no avail and "has contributed more to [Haber's] modesty than to [his] success." Haber's deteriorating health added a reason of its own for the need to postpone his trip to Palestine:

> Meanwhile, the condition of my heart is changing with the coming winter and increasing anxiety, and the thought that seemed self-evident to me, namely that I could take off for and reach Palestine in order to recuperate, has now changed due to my state of health into its very opposite. … I presumed that you would travel to Palestine for Easter [sic] and inquired here with a physician about the possibility of going to Madeira this month. He warned me against this journey as too great an undertaking and has thereby implicitly forbidden my trip to Haifa. Added to the concern that the German authorities will cause me trouble when I'm far away is a new and greater fear that the trip would not improve but rather worsen my condition.

As for the latter, Haber offered the following reflections on Weizmann's project, Jewish history, and Zionism:

> In truth, I do not envy you your great project. I feel with increasing urgency every day that only those things are worth doing that we venture to do out of a higher consideration. But for that we need strength and confidence in our physical endurance, and it seems to me that the conditions for your success depend increasingly on overcoming an inner deficiency of the Jews in my homeland that has not yet been stamped out by Hitler's Germany. [The German Jews] feel closer to the German state than to Zionism and [live] without the purity and simplicity of a spiritual direction of their own. Since Hitler's economic policy was met with success, the days of the Jewish prophets faded in the fog of a forgotten past and the overrating of a physically bearable existence has moved into the foreground of their interests again. No one who preaches from his desk about the Maccabees can escape being laughable, but no one who expects peaceful citizens to turn into Maccabees can escape a madhouse. I have known the wartime battlefields on which French and English Jews shot German Jews, just as French and English socialists shot German social democrats and that left behind strains of mortality that are painful to bear [a paraphrase of Goethe's Faust, verse 11954].
>
> The Russian Jews are ahead of us, because they suffered during the days when in Germany we were seeking honor and respect. If the Americans recover economically, they will become Zionists again, as they had been before the Hitler-days. But if their system of private capitalism fails, Palestine will have to make its ascent not with the help of [American] means but, in accordance with Bismarck's dictum, by means of blood and iron. I'm writing all this not as an opinion of a man who feels responsible but from the perspective of the age that the year 1933 has bestowed on me and with the wish to be as useful to you as my strengths allow and with my all best wishes for your success and the well-being of your family that has instilled a feeling of true friendship in my tired soul.

No record of Weizmann's reaction to this letter from Haber has been found. In his next letter to Weizmann, Haber recounted the emotional problems he faced when submerged in a foreign culture in Cambridge – with repercussions for his ever more distant plans to move to Palestine [22]:

> I'm afraid I haven't made myself sufficiently clear about what it means to move at my age to a land with a foreign language and way of life. I enjoy here all the conceivable formal friendship in the circle of fellow chemists. But I miss all those natural leadership activities that I had developed at home over 40 years. Whether I will be able to step out of this circle, in which you still enjoy a great deal of respect since your Manchester days, during this winter and conceive of anything other than a sojourn in a foreign sanitarium is as uncertain as crossing a lake on thin ice.

Before his departure from Cambridge, Haber wrote a letter addressed to the vice-chancellor of the University in which he stressed that the "chivalry from King Arthur's time still [lived] among [English] scientists" and expressed a "strong hope" that he "will be able to return within a few weeks" to Cambridge [5, pp. 615-616]. At this time of humility and contrition, Haber also drafted his will. In it, he expressed his wish to be buried alongside his first wife Clara, in Dahlem, if possible, or elsewhere "if impossible or disagreeable" [5, p. 630].

Fifth and final meeting (London, 26 January 1934)

Haber departed from Cambridge on 26 January 1934. During a break in London the same day, he met Weizmann for the last time. Haber's son Hermann and Weizmann's brother-in-law Josef Blumenfeld were also present, as at the first meeting between Haber and Weizmann in London less than two years earlier. Not much is known about what was discussed at this meeting. Haber was weak and exhausted and Weizmann must have realized that Haber would not be joining him in Palestine any time soon. Following their final meeting, Haber took off for Orsellina in southern Switzerland. At a stopover in Basle, he was joined by his son Hermann and his wife Marga as well as by Rudolf Stern and his wife. Haber passed away, as a result of heart failure, in the evening of the same

day, 29 January 1934, in his room at Hotel Euler in Basle [14, p.102].

In his condolence telegram addressed to Hermann Haber, Weizmann stated [23]:

> Deeply shocked and distressed sad news your dear father's death science and humanity lose in him one of their greatest sons.

Einstein noted in his letter to Hermann and Marga that Haber's was "the tragedy of the German Jew: the tragedy of unrequited love" [24].

On 3 April 1934, the Daniel Sieff Research Institute was inaugurated, with Weizmann as its founding director [25]. Richard Willstätter gave the inaugural speech, in which he extolled Weizmann's accomplishments and remembered his friend Haber. The next day, on 4 April 1934, a cornerstone was laid for the institute's library building. Among those in attendance were, apart from the host Chaim Weizmann, Ladislaus Farkas, visiting from Jerusalem, and possibly Haber's stepsister Else Freyhan. The new library building would provide a home for Fritz Haber's book collection, bequeathed to the Sieff Institute by Hermann Haber. The original library of the Sieff Institute, named after Fritz Haber, was inaugurated on the second anniversary of Haber's death, 29 January 1936 [26]. Today, the Fritz Haber Collection is a part of the main library of the Weizmann Institute of Science in Rehovot. It consists of science classics from Haber's time, often with a personal inscription by the author.

3. Epilogue

In his autobiography, published fifteen years after Haber's death, Weizmann characterized Haber as someone "who *was* [our emphasis] lacking in any Jewish self-respect. He had converted to Christianity and had pulled all his family with him along the road to apostasy" [1, p.352]. We wonder whether Weizmann, after witnessing at close range Haber's "reconversion" to Jewish secularism and his growing sympathies for Zionism, did not mean to say "had been" instead of "was." As Stefan Wolff pointed out, Haber in fact never stopped caring for Jews – and anti-Semitism remained his major concern. However, he had additional concerns and identities. Haber's conversion, at age twenty-three, happened in the aftermath of the public debate between an overt anti-Semite, Heinrich von Treitschke (1834–1896), and a liberal, Theodore Mommsen (1817–1903). The latter called upon Germans to abandon "those loyalties and affiliations that divided them" [27]. Haber's embrace of Protestantism, to which he was exposed since high school, may have also been motivated by Greek philosophy, which he studied passionately, especially Plato, with his emphasis on the spirit [28]. According to Rudolf Stern's testimonial, "one has no right to throw doubt on the integrity of [Haber's] motives [for conversion]. It would be ridiculous to interpret his conversion as caused by ambition and opportunism, for it was performed at a period when Haber did not dream of an academic career but was firmly resolved to take over and enlarge the family business" [14, p. 88]. However, Willstätter rebuffed conversion for whatever reason, on principle: "One has to refrain from conversion to Christianity, 'because it is connected with rewards' [quoting Walter Rathenau]" [29, p. 396]. Regardless of their differences – between them and with him – Weizmann cherished the memory of both Haber and Willstätter: In his office at the Sieff Institute, he kept, displayed side by side on his desk, their photographs, see

Figure 3. Their silent presence speaks volumes to curious visitors of Weizmann's quarters, now that they have been converted into a historic site.

Figure 3. Chaim Weizmann in his office at the Sieff Institute in Rehovot. Seated at his desk, Weizmann is flanked by photographs of Fritz Haber and Richard Willstätter. The picture was taken at Weizmann's press conference on 26 February 1945. P. Goldmann, Weizmann Archives.

Note on availability:

The letters held at the Weizmann Archives are available online at https://www.weizmann-archives.org.il/.

Note concerning translations:

All translations from German into English appearing in this article are our own.

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Life as a child in Poland in World War II

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Asher Mandelbaum (1934 – 2020)

I was born in Krakow, Poland, in late December 1934. World War II broke out when I was nearly five years old and it changed the entire course of our lives. When the war erupted, my father happened to be in Lvov on business. The city was occupied by the Russians and he was exiled to labor camps in Siberia and Uzbekistan. When Krakow was occupied by the Germans (in September 1939) my mother took me and my younger sister Dina to her parents in Koszyce, a small town about 50 km from Krakow.

Edicts against the Jewish community were published a short time after we arrived in Koszyce. The synagogues were closed and it was forbidden to pray together even in private homes. The Jewish school was closed and the education of Jewish children was prohibited in any form or setting. A short time after the occupation, Jews became obliged to wear identification tags (a blue Star of David) on their sleeves. Towards the winter of 1941, the occupying forces confiscated all furs belonging to Jews and these were transferred to the German army stationed on the Eastern front. Various limitations were set on the employment of Jews, and the Jewish Committee was often required to pay fines. In the second half of 1942, all Jews residing in the cities and towns were concentrated in ghettos and concentration camps and their final extermination began. The Jewish Committee in Koszyce succeeded in postponing the deportation a couple of times until November 1942 by bribing the German commander.

In the period preceding the deportation, my grandfather, Yaakov Kaminsky, contacted a young Pole, Janek Młynarczyk, from the small village of Górka near Koszyce, who was ready to help save our family. To this day, I cannot understand why Janek agreed to assume this dangerous and difficult task. The German authorities declared that helping Jews would result in a death sentence, both for those guilty of providing assistance and for their entire families. I have never received a satisfying answer to this conundrum despite my correspondence with Janek and his wife and a long conversation with them in Poland in 1998. His great appreciation for my grandfather was apparent and he repeatedly declared that he did what he did "because Pan Kaminsky said so".

On a night in November 1942, the Jews of Koszyce were gathered in the town square and taken in trucks to a concentration camp, where nearly all of them were killed. The night before, Janek had transferred our family to his uncle's house in the small village of Szczelce. Fifteen people crowded together into a dark cellar: my mother, my four-year-old sister, myself (eight years old), my grandmother and other relatives. My grandfather, who was a member of the Jewish Committee, did not join us. He was taken to the concentration camp with the other Jews of Koszyce, where he died.

After about two weeks in Szczelce, Janek transferred us to the ghetto the Nazis had formed in the town of Bochnia, about 50 km from Krakow, where we spent the winter of 1942/3. I remember that the ghetto was terribly crowded, both in the living quarters and in the streets. The winter was extremely cold and means of heating were very scarce. There was also a constant shortage of food. The most difficult problem was our uncertainty regarding the future. Towards the spring of 1942, rumors abounded about the approaching liquidation of the ghetto.

Despite the dangers, Janek succeeded in entering the ghetto and consulting with my grandmother and mother concerning our next moves. In light of the constant rumors, it seemed that it would be dangerous to remain and we must find another solution. They felt that my grandmother, my sister and my grandmother's sister looked sufficiently Polish to enable them to acquire false identities and present themselves as Poles in distant locations, where there was no reasonable chance of meeting acquaintances. Equipped with false documents they moved to Warsaw, where they remained until the partisan revolt in 1944. However, my mother and I looked Jewish and could not avail ourselves of this solution so we needed to find a hiding place.

The first stage was to leave the ghetto. Janek succeeded in bribing a German officer (not an easy venture, but it is beyond the scope of this short summary), and on an evening in May 1943 I left the Bochnia ghetto with my mother in a German army car and we arrived on the outskirts of the village of Szczurowa, between Bochnia and Koszyce. Janek was waiting for us nearby and he led us in the dark to a small wooden hut belonging to his relatives. The hut consisted of only one room with a little attic and it was occupied by three brothers. They used the only downstairs room and we received the attic, which could only be reached by ladder. Janek was aware of the anti-Semitic views of his fellow Poles (and of his own relatives) and he introduced us as political refugees fleeing the occupying forces and warned us to avoid any mark of Jewishness.

One evening, after we had been in this hiding place for about two weeks, my mother heard the brothers discussing us at supper and sensed that they suspected we were Jews. She decided that it would be dangerous to remain there, and when our hosts fell asleep we left the hut. The only person we could trust was Janek and we set out to find him. After walking all night on unknown and unmarked roads, encountering German patrols which luckily did not identify us, we reached Górka early in the morning. We were forced to ask local villagers working in the fields for directions to Janek's home. Our ordeals throughout this day are engraved in my memory as one of the most terrifying days of my life, although it will not be possible to relate everything that happened to us here.

At this stage, Janek began seeking a permanent hiding place for us. Over the next three-four weeks, he would find us temporary hiding places in friends' or relatives' barns or cellars for two-three days, where we hid in haystacks or heaps of litter; however I do not remember this period in detail. I remember the fear of our "hosts" (which was justified, considering the death penalty for those caught harboring fugitives and for their families), who brought us food upon our arrival (usually a three-day supply of bread and water) and hurried to leave home for the duration of our stay. Sometimes we found that mice had eaten from our bread. I also remember the terrible fear of moving from one hiding place to another, in the dark, at the age of 8½.

In July 1943 Janek found us a hiding place in the remote village of Młynarczyk, approximately three km from Koszyce, at the home of a church organ player, Mr. Elias, who was acquainted with my grandfather. From the beginning of the war, Mr. Elias' daughter, son-in-law and their three daughters, the Skowron family, had been staying with him, having fled Warsaw when the war broke out. Mr. Skowron had previously been employed as a civil servant and he had been a member of the fascist Polish National Democratic party (EnDe). During the war he was active in the right-wing partisan Resistance "Armia Krajowa" known for its anti-Semitism, and he stored arms and ammunition for the partisans in a small shed in his father-in-law's house. Discovery of this shed and its contents by the Germans would undoubtedly have brought the death penalty upon the entire family. Therefore, Janek assumed that it would be easier to convince them to hide us in the shed. At first, Mr. Elias strongly objected, but upon hearing that my mother was the daughter of Mr. Kaminsky he gradually relented. The fee that was promised also contributed to his decision.

I will attempt to describe the designated hiding place. It was about two meters long and a maximum of 1½ meters wide. A wide wooden plank slightly less than two meters long was placed on two barrels along the length of the shed, covered by a few sacks of straw. This plank, which occupied most of the shed, served as our bed, table, bench, and everything else. Opposite this bed, along the shed's wall, were shelves heaped with arms and ammunition. Above the "bed" Mr. Skowron installed a larger shelf for us, which served us as a table and work surface. He blocked the entrance to the shed with planks and hid it from strange eyes. He also uprooted a few planks from the floor of the dining room, which bordered with the bunker, and he dug a small tunnel under the floor through which it was possible to crawl. This tunnel served for the daily passage of food and water and the removal of our waste. The bunker's "furniture" ("table", "bed" and shelves) and the tunnel opening left hardly any free space to stand or walk.

Our bunker allowed no light. Rachwałowice, similar to most Polish villages at the time, was not connected to the electricity network (there was also no running water or telephones), and there was a shortage of fuel due to the war. Skowron brought us a carbide lamp, which gave off white light which enabled some activity in these harsh conditions. The operation of this lamp was probably my first chemical experiment:

$$\underset{\text{calcium carbide}}{CaC_2} + H_2O \rightarrow \underset{\text{acetylene}}{HCCH} + CaO$$

A tap is opened, causing contact between carbide and water and the formation of acetylene, and when the latter burns it produces an open light. Under normal conditions, I would not advise using such a lamp for lighting purposes, certainly not in a small closed room. At the time, the carbide lamp was an essential part of our mental survival.

We hid in this bunker for a year and a half, from July 1943 until the second half of January 1945. We had two books, the first was the famous classical poem "Pan Tadeusz" by Adam Mickiewicz, and the second was a geographical encyclopedia. I read both books many times, and by the time of our liberation,

I almost knew "Pan Tadeusz" by heart. Another occupation was knitting sweaters and socks for the Skowron family and for ourselves. I acquired a not insignificant proficiency in this craft. Under Janek's direction, Mr. Skowron bought the wool in small quantities in a distant town in order to avoid attracting the neighbors' attention. He used this method for other shopping as well.

Throughout our prolonged stay in the bunker, my mother devoted much time to teaching me as many subjects and topics as she could in the absence of textbooks. She taught me the Hebrew alphabet, and also prayers she knew by rote. During the months of September-October and April she asked Mr. Skowron about changes in the shape of the moon, and accordingly estimated when Yom Kippur and Pesach occurred; she fasted on the former and avoided eating bread during the latter.

Due to Mr. Skowron's membership in the Resistance we received news bulletins with information about the various fronts. I remember our joy on a morning in June 1944, when we heard about the allied forces' landing in Normandy (6.6.1944). From here on, the news we heard signaled that the end of the war was near and with it the end of our troubles.

One night we heard the frightening noise of an airplane. Skowron told us that that night a British plane had landed near the cemetery of Rachwałowice, unloaded a shipment of arms and a high-powered transmitter, and left carrying one of the Resistance leaders. Skowron brought some of the equipment to our bunker, luckily not assisted by his comrades. This sign from the free world gave us a wonderful feeling but we were also frightened of possible German searches as they had probably noticed the planes as well.

The Red Army offensive began towards the end of 1944. After waiting for about a year on the eastern bank of the Vistula (Wisla), they crossed the river at a number of points and drew near us. The German army started to retreat, and many trucks passed Rachwałowice on their way west, very close to our hiding place. Skowron reported with concern that the Germans wished to establish their headquarters in Rachwałowice, and that the village chief had offered them our house. For three days the Skowrons deliberated how to solve the problem, which could put their entire family (and us too) in risk of facing a firing squad, although we were so close to liberation. Luckily, the German commander thought that the house of the village chief would be a more suitable headquarters, thereby solving one of the most serious threats to our survival. But the danger was not yet over. Two German officers were stationed at our house, and the room they chose was the dining room that bordered with our bunker, into which our tunnel opened. It was terrifying to hear the hobnailed boots of our neighbors on the other side of the wall. The Skowrons were frightened too, lest the officers would discover the tunnel's opening, and reduced their contact with us to bringing water and food and removing our waste.

In early January 1945, close to my tenth birthday, the German army began their panicked flight westwards. In our area, they suffered a shortage of fuel, and in their flight they used horses and carts confiscated from villages on the way. Although the bunker was impermeable, we heard them prodding the horses past our house for three days and three nights.

Krakow was liberated by the Red Army on January 19th 1945, and the Russians arrived in Rachwałowice a few days later. Skowron made a small loophole for us in the blocked opening of the bunker so that we could see the Russian tanks passing through the village. Only the next day did Skowron allow us to leave the bunker for the dining room, and even then only for limited periods of time. Our elation upon our liberation is indescribable and I'm not certain that I can faithfully reconstruct my feelings on this special occasion. Our renewed encounter with daylight after sitting for a year and a half in a sealed bunker was a very special experience. I remember how difficult it was for me to leave the window, the view of the white winter country and the blue sky.

Our joy at the war's ending was mixed with serious questions with regard to our first steps after leaving the bunker, having been completely severed from normal life for such a long time. Janek advised us to wait a couple of days at the Skowrons, to see what would happen, and then to move to Koszyce, at least temporarily. He spoke to the family that lived in my grandfather's spacious house (the Glowacz family), and received their consent for us to stay there for some time. In the meantime, the Skowrons did their utmost to keep our existence hidden from their anti-Semitic neighbors, who might have killed them and us all.

A couple of days after the liberation, early on a cold and snowy Sunday, when all the villagers were still asleep, we left on foot for Koszyce, a distance of about three km. After a while I could not continue walking. A year and a half in a small bunker without movement had caused my muscles to atrophy, making it very difficult to walk. Skowron carried me for most of the way (I did not weigh much), and thus we arrived that morning in Koszyce. Janek directed my grandmother and my sister (whom he had also cared for throughout that period) to Koszyce as well and took us all by horse and carriage to Krakow, a distance of about 50 km. A few holocaust survivors who had succeeded in remaining alive gathered together – some had survived in hiding, some with the Resistance or in concentration camps. Immediately after the war, the refugees established a Jewish committee which took care of

all their needs, for example living quarters, jobs, reactivating synagogues, founding and operating Jewish schools, etc. At the Jewish school "Tarbut" we studied intensively for three years in order to complete all the material we had missed during the war. In the summer of 1946, my father returned from Russia and our family was reunited after being separated for almost seven years.

Janek's contribution to our rescue was crucial, although, as I have mentioned, to this day we do not know the motivation for his actions. Throughout the entire period, he was exposed to daily life-threatening danger in his attempts to find us short- and long-term hiding places, transferring us from one hiding place to the other, by foot or by carriage, and locating money that my grandfather had deposited with neighbors with whom he was befriended, to pay for our monthly lodgings and my grandmother and sister's expenses in Warsaw. Yanek and the Skowrons were acknowledged as righteous gentiles by "Yad Vashem".

In early 1948, a short time after my bar-mitzvah, our family received permission to leave Poland. In March of that year we left Poland for France. After a short stay in Paris we traveled to the sea port of Marseilles, where we joined a Jewish Agency immigrants' camp. We arrived in Israel on the French boat "Providence" as part of the "Aliya D", equipped with a real Polish passport, a real visa to Bolivia (purchased from the Consul in Paris), a false transit visa through Palestine and the address of an imaginary relative in Tel-Aviv, whom we were allegedly going to visit on our way to Bolivia. We were on the deck of the boat on Friday, Iyar 5th, May 14th, 1948, when we heard over the loudspeakers that the State of Israel had been established. Our joy was subdued; we all knew that a new war was about to begin, three years after the terrible last war had ended. The next day we reached the Port of Haifa, from where we were taken to the immigration camp in the sands of Kiryat Shmuel (present day Kiryat Yam), and about two weeks later we moved to a rental apartment in Haifa.

At this point a new chapter began in my life. In the autumn of 1948, I began my studies in Israel at the "Netzah Yisrael" school in Haifa, where I enrolled in the 8th grade. During the years 1949-1953, I studied at the religious "Yavneh" high school in Haifa and after my military service during 1953-1955, I began studying at the Technion Faculty of Chemical Engineering.

During the second year of my studies I participated in two courses in organic chemistry given by the late Prof. David Ginzburg. The courses were jointly addressed to students of the Faculty of Chemical Engineering (about 70 students) and students of the Faculty of Sciences – Chemistry (about 10 students). Professor Ginzburg succeeded in transforming the study of organic chemistry into the most fascinating experience, and as a result I decided towards the end of my second year to transfer to the Faculty of Sciences – Chemistry, which later became the Faculty of Chemistry.

In November 1958 my life changed when I married Leah Faber, who was (and still is) my sister's best friend. In 1960 and 1961 our two sons, Moshe and Yitzhak, were born, and in 1967 and 1969 our two daughters, Aviva and Ilana.

In 1959, I finished my undergraduate studies and received my BSc. About a year later I received the degree of MSc for developing a new method for synthesis of triphenylenes, supervised by Dr. Michael Cais, a new faculty member. Prof. Cais served as the supervisor also for my doctorate thesis (1960-1963) on isolating and determining the structure of the components of the narcotic plant Catha Edulis. In this research, we used mass spectrometry to determine the molecular weight and structure of one of the plant's components. Since in 1963 there was no mass spectrometer with the capacity to measure high molecular weights (up to 1000 dalton) in Israel, the mass spectra were measured in the laboratory of Prof. Carl Djerassi at Stanford University in the US. Following the success of this method for determining the structure of organic materials, Prof. Ginsburg decided to establish an organic mass spectrometry laboratory at the Technion. Towards the end of 1963, an Atlas CH4 mass spectrometer was purchased, and I was offered to serve as a faculty staff member with the rank of lecturer and as head of the new laboratory.

One of the first projects we performed with the new equipment was investigating the fragmentation of various derivatives of morphine, provided by Prof. Ginzburg from his large collection. Amongst the materials examined were a number of stereoisomers differing in the configuration at position 14 of the morphine system. To our surprise, the mass spectra of the stereoisomers were entirely different, and the differences indicated stereospecific fragmentation mechanisms. The standard opinion at the time was that due to the relatively high energy in the electronic ionization process, the ions created undergo isomerization to the most stable structures, and therefore there should be no expectation of differences between the mass spectra of stereoisomers. This view was disproved by our observation, which later led to many studies performed by the Technion's mass spectrometry group.

Prof. Mandelbaum passed away on 21st June, 2020. Further details of his academic career can be found at https://chemistry.technion.ac.il/wp-content/uploads/2019/10/Memoirs_September_2019-1_compressednew-1.pdf

Dining with great chemists

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This is a story with several contributing segments all of which merge at the end.

In the course of my PhD studies under the direction of Nobel Prize Laureate Prof. Donald Cram, I was involved in studies dealing with optically active sulfur compounds.

Upon graduation, I went for an interview with the pharmaceutical company Wyeth Laboratories in PA. After they had shown me the place they brought me to Dr. Herchel Smith the head of research. Dr. Smith asked me if was interested in joining Wyeth to which I asked on what basis was he offering me a job since I had not been requested to give a seminar and no one had asked me any relevant questions during my tour of the company. Dr. Smith replied that he had received a good recommendation for me from Prof. Cram and that was sufficient for him. I did join Wyeth.

Since I did not eat in the cafeteria, I spent my lunchtime in the library where I accumulated enough data, dealing with optically active sulfur compounds, to write a review in this field. I then contacted Dr. Norman Kharash, the editor of the journal *International Journal of Sulfur Chemistry* and asked him whether he would publish the review, to which he replied positively. Subsequently, I submitted a second review on this field, which was also published by Kharash. Eventually after publishing four reviews, I contacted Kharash with the fifth one suggesting we should unite all five reviews as individual chapters in a book, which was published as the *Chemistry of Optically Active Compounds*.

My immediate supervisor at Wyeth was a former student of Prof. E. J. Corey at Harvard. In 1972, I attended an American Chemical Society meeting where Prof. Corey was the keynote speaker lecturing on "Logic and heuristics applied to synthetic analysis," since he had invented the first computerized program for retrosynthesis. This was probably the earliest version of programs developed by SciFinder. While listening to Corey's lecture, I noticed that a senior gentleman a couple of rows behind me was happily having a good nap. At the end of the lecture I went up to the podium to give Prof. Corey regards from my supervisor. While speaking to Corey the sleepy gentleman came up and effusively congratulated Corey on the wonderful lecture presented. He then turned to me and exclaimed "Abraham, how are you," this was none other than Norman Kharash, who then asked me what my plans were and I answered that I was planning to go to see my former colleagues at UCLA. Kharash then insisted that I had to join him for lunch. As we were exiting the lecture hall, a gentleman approached us, and Kharash greeted him enthusiastically saying "Prof. Birch how are you? Where are you going." Prof. Arthur Birch replied that he was going to grab a bite, to which Kharash insisted that he join us for lunch. Now I was accompanied by two renowned chemists, whereas I was a relatively recent PhD graduate.

We went to a restaurant on Sunset Strip, and when the waiter showed us the menu I realized there was nothing kosher to eat, so I asked him whether it would be possible to have a green salad. The waiter told me that they did not have such, to which Karsh interceded and requested to see the chef. So,

Abraham Nudelman was born in Mexico, and received his BSc from Bar-Ilan University, MSc from Brooklyn College and PhD from UCLA under the direction of Nobel Laureate Professor Donald Cram. After several years in the pharmaceutical industry, he returned to Israel. After six years at the Weizmann Institute, he established the Division of Medicinal Chemistry in Bar-Ilan's Chemistry department. He became a Professor Emeritus in 2008 and still maintains an active lab. He was appointed an Honorable Member of the ICS in 2019.

the chef with his high, white cylinder appeared by our table and Kharash asked him whether he could prepare a salad for me. The answer was positive and a short while later, the chef himself brought the most exquisite and elaborate salad I have ever seen. Everyone around was looking to see who was deserving of such a delight.

Another part of the story relates to the fact the Herchel Smith had been Arthur Birch's student, and in the course of his studies, using the famous *Birch reduction reaction* as a key step, developed a total synthesis for a steroid. In those days if a student invented something at Cambridge University, he could take the invention with him and patent it without needing to inform the university. Herchel Smith took his patent and sold it to Wyeth Laboratories, that developed the steroid into Ovral – Levonorgestrel. This drug became the most popular oral contraceptive in the world. In addition to the substantial sums that Dr. Smith received from Wyeth as royalties for his invention, he was also nominated as head of research, and that is how I became a medicinal chemist at Wyeth. By the way, from the royalties received from Wyeth, Dr. Smith donated over US $200 million to Cambridge and US $100 million to Harvard.

Now, while we were sitting at the table Kharash, Birch and me eating my salad, the conversation shifted to my place of employment. However, when I mentioned to Arthur Birch that Herchel Smith was the person who hired me, he turned all red and upset. This was due to the fact that Herchel, who had used the Birch reduction in the steroid synthesis, had not bothered to put Birch's name on the patent as a co-inventor, even though he had been involved in steroid synthesis, and therefore Birch did not get any of the royalties. You can imagine that I quickly shifted the course of the conversation.

It would be a disservice not to mention that Prof. Cram had a custom of inviting all his students every year for a barbeque dinner in his estate, which was a most enjoyable event, although all I could eat were some peanuts and raisins. One year after Prof. Cram announced the dinner date and invited us all, I went up to him and indicated that regretfully I would not be able to join that year because the date of the dinner fell on Shavuot. Without hesitation, Prof. Cram told me that the tradition of his dinners went back 20 years, whereas my Shavuot tradition went back thousands of years and, therefore, I won. He proceeded then to contact all the students and postpone the dinner to another date so that I would be able to attend and have my portion of peanuts and raisins.

This short story is a reminder of how fortunate I was to be in close contact with powerful, excellent chemists such as Herchel Smith, Donald Cram, E. J. Corey, and Arthur Birch. By the way, shortly thereafter, Herchel Smith quit Wyeth and became a granting consultant for the USA government at a salary of $1/year.

Interview with Prof. Abraham Nudelman – 2019 Honorable Member of the ICS

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Q: Tell me a little about your personal history.
A: I was born in Mexico and came to Bar-Ilan University in 1957 as an undergraduate after finishing high school. After graduation from Bar-Ilan, I went to Brooklyn College in NY where I received an MSc degree in chemistry under the direction of Prof. Paul Haberfield in 1964. From Brooklyn College, I went to UCLA and got a PhD in chemistry in 1969 under the direction of Nobel Prize Laureate Prof. Donald Cram. Upon graduation I joined the pharmaceutical company Wyeth Laboratories in Pennsylvania and worked there till 1975 when my family and I returned to Israel. I then worked for six years at the Weizmann Institute of Science and subsequently joined the Chemistry Department of Bar-Ilan University where I established the Division of Medicinal Chemistry, unique to Bar-Ilan. I worked in Bar-Ilan from 1981 reaching the rank of full professor and retired in 2008. My lab in Bar-Ilan is still functioning and I continue together with my assistants in my investigations in various fields of medicinal chemistry and drug development.

Q: What inspired you to study chemistry?
A: I had a good chemistry teacher in high school and a cousin of mine inspired me to pursue chemistry since he himself was a chemist and worked in the pharmaceutical company Syntex, first in Mexico and then in San Francisco.

Q: What attracted you to an academic career?
A: After working in industry for six years and as an investigator for another six years and considering that I had taught medicinal chemistry courses at the Weizmann Institute, I decided it was time for a change and that led me to an academic position at Bar-Ilan University.

Q: Who were your role models?
A: Prof. Donald Cram of course. I much admired Prof. Gilbert Stork's work at Columbia University and that of Dr. Herschel Smith, the Director of Research at Wyeth Labs., who

Arlene Wilson-Gordon was born in Glasgow, Scotland. She completed her BSc (Hons) at Glasgow University and her DPhil at Oxford University under the supervision of Peter Atkins. After a postdoc at the Hebrew University with Raphy Levine, she joined the faculty at the Department of Chemistry, Bar- Ilan University, where she rose to the rank of Professor and in 2015, Professor Emerita. Her research interests lie in the field of theoretical quantum and nonlinear optics. She is the editor of the Israel Chemist and Engineer, an online magazine for all who are interested in chemistry and chemical engineering.

discovered the oral contraceptive Ovral – Norgestrel, which became the most popular contraceptive in the world. I have to mention also Prof. Shmuel Sprecher who was my main chemistry teacher at Bar-Ilan and taught me General and Inorganic Chemistry, Organic Chemistry and Mechanisms in Organic Chemistry.

Q: Why did you choose your particular field of research?
A: I had worked at Wyeth Laboratories in a variety of areas of medicinal chemistry and was inspired by the beauty of the organic chemistry needed for the synthesis of new biologically active molecules, so the field of medicinal chemistry was an obvious area of research.

Q: Do you enjoy teaching and interacting with students?
A: Most definitely, I thoroughly enjoy teaching and delight when I see a student's smile after understanding a complicated feature of the material.

Q: Do you have former students whose achievements you admire?
A: I have been fortunate that a considerable number of my former MSc and PhD students have reached good positions in a variety of fields in industry and research institutions. These include Lilach Hedvati who served as head of the generic drug synthesis at Teva Pharmaceuticals; Shani Zeeli a patent attorney; Dana Mizrachi who holds a senior position at the Biological Institute of Nes Ziona; Ayelet Nudelman, my former student and present daughter-in-law, who is a senior analytical chemist at Analyst Research Laboratories; Michal Weitman Head of the Mass Spectrum unit at Bar-Ilan; Bilha Fischer and Amnon Albeck who are medicinal chemistry professors at Bar-Ilan – Amnon is now Rector and Bilha is Dean of Exact Sciences; Dvir Doron associate director of chemical and computational toxicology at Teva Pharmaceuticals; and Inessa Yanovski who is a researcher in the Chemistry Department of Bar-Ilan.

Q: What were the main difficulties you encountered in your research and how did you overcome them?
A: With the exception of a few highly unpleasant characters whom I encountered, I was lucky to be able to conduct my investigations in a generally pleasant manner, collaborating with good scientists both in Israel as well as abroad. This work led to the discovery of a significant number of biologically active substances in areas of cancer, bacteriology, schizophrenia, analgesia, sickle-cell anemia, inflammation, AIDS and others.

Q: What do you consider your greatest scientific achievement, so far?
A: Three of my compounds reached the stage of human clinical trials. The compounds labeled AN-9 as an anticancer agent, AN-10 as a substance that increased fetal hemoglobin and AN-168 as an antischizophrenic drug. Presently, I am collaborating with Israel Prize Laureate, Prof. Marta Rosin, from the Hebrew University and we have discovered a family of extremely potent anti-inflammatory agents which have been patented and are at the preclinical stage. Another active collaboration is with Dr. Betty Pace from the Augusta University in Georgia, USA, where we are evaluating one of my compounds for the treatment of sickle-cell anemia.
In the course of my student Yaakov Herzing's PhD studies, we discovered a new chemical reaction that we applied to a novel patentable procedure for the synthesis of the anticancer agent Etoposide. Based on this synthetic method, Teva Pharmaceuticals developed an industrial process for the synthesis of Etoposide and marketed the compound for many years.

In addition, I came up with the idea of creating a list of the H^1 and C^{13} NMR chemical shifts of common solvents. In collaboration with Dr. Hugo Gottlieb, this work was published as "*NMR chemical shifts of common laboratory solvents as trace impurities*" in the *Journal of Organic Chemistry* in 1997. This article has become the MOST READ article in the history of the *Journal of Organic Chemistry* with close to 660,000 "reads". It has been cited thousands of times and to the best of my understanding has been printed innumerable times by chemists worldwide who use the table most frequently, and has been incorporated into the catalogs of manufacturers of NMR equipment. Subsequently, in collaboration with investigators from Washington University and Caltech, a second publication entitled "*NMR chemical shifts of trace impurities: Common laboratory solvents, organics, and gases in deuterated solvents relevant to the organometallic chemist*" appeared in the journal *Organometallics* in 2010, which combined the data of our first publication with similar data related to solvents used in organometallic NMR studies. This publication also become the MOST READ in O*rganometallics,* and both publications combined have become "Most Read" more than 1,100,000 times. The story of this original idea was further advanced when we were approached by investigators from Smith-Kline-Beacham Pharmaceuticals and published with them the third paper in the series, entitled "*Development of GSK's NMR Guides – A tool to encourage the use of more sustainable solvents*", in *Green Chemistry* in 2016, this time including NMR spectra of particular solvents used in industry and "green" solvents.

Q: What do you consider to be your greatest contribution to Israeli society?
A: I have been fortunate to be able to advise a good number of students who eventually became very successful and continue to serve society in a highly positive manner.

Q: Would you recommend a scientific career to young people?
A: Yes, provided they have a lot of stamina and patience, and the ability to interact with students, staff, university bureaucracy and granting institutions.
Q: If you had a magic wand, what would you change a) in academic life, b) in Israeli society?
A: In Israeli society, I would change the way people and parties are elected to the Knesset. If I could, I would attempt to reduce inequality in education, army service and salaries. I would love to reduce the extremes, both from religious as well as political positions. I dream I could see people who are well-behaved, clean, not pushy, considerate of their surroundings.

Q: Do you have any advice for young people embarking on their career?
A: Try to get involved in something that really interests you. Expect to encounter all types of people in your career, from intelligent, cooperative and pleasant to jealous, miserable, lazy and incompetent characters. Try to keep up your best standards but at times be willing to compromise.

Q: Do you have any hobbies or interests apart from your scientific work?
A: I love Spanish poetry, classical music and geography.