

Evolution of Patch Testing

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THE HISTORICAL ASPECTS of patch testing were reviewed by Foussereau.¹ A selection of important steps forward is reviewed here, with the focus mainly on the outstanding contribution of some masters in the field in earlier years.

Initial Approach to Patch Testing

During the seventeenth, eighteenth, and nineteenth centuries,¹ some researchers occasionally reproduced contact dermatitis by applying the responsible agent (chemical, plant, etc.) to intact skin. Although most of the observations are anecdotal, some deserve special attention.

In 1847, Städelers described a method for reproducing on human skin the lesions provoked by *Anacardium occidentale* (Städelers blotting paper strip technique). This method was described as follows: “Balsam is applied to the lower part of the thorax on an area measuring about 1 square centimeter. Then a piece of blotting paper previously dipped in the balsam is applied to the same site. Fifteen minutes later, the subject experiences a burning sensation, which increases very rapidly and culminates about half an hour after. The skin under the blotting paper turns whitish and is surrounded by a red halo. As the burning sensation decreases, the blotting paper is kept in place for 3 hours.”² This observation is important because this was the first time that any test was actually designed and described in full detail.

In 1884, Neisser³ reviewed a series of eight cases of iodoform dermatitis triggered by iodoform application. The symptoms were similar to those subsequent to the application of mercurial derivatives, and a spread of the

lesions that was much wider than the application site was a common feature.

In retrospect, this presentation can be considered an important link between casuistical writings of older times and a more scientifically oriented approach to skin reactions provoked by contactants. It was a half-hidden event that heralded a new era that blossomed at the end of the nineteenth century.

Josef Jadassohn, Father of Patch Testing

Josef Jadassohn (Fig 1) is universally acknowledged as the father of patch testing (“funktionelle Hautprüfung”), a new diagnostic tool offered to dermatologists.⁴ At the time of his discovery, Jadassohn was a young professor of dermatology at Breslau University in Germany; he most probably applied and expanded—in a practical way—observations and interpretations previously made by his teacher, Neisser.³ Summing up the different sources of information available, we can reasonably assume that (1) the patch test was born on Monday, September 23, 1895, at the Fifth Congress of the German Dermatologic Association held in Graz, Austria, where Jadassohn made his oral presentation “Improving the Knowledge of Drug Skin Reactions,” and (2) the “birth certificate” is dated 1896, when the proceedings of the meeting were published.⁵

As recorded by Sulzberger in 1940 in his classic textbook,⁶ the key message of Jadassohn’s paper was the fact that he recognized the process of delayed hypersensitivity to simple chemicals.

Concerning the technical aspects of the “funktionelle Hautprüfung,” the methodology was quite simple: gray mercury ointment was applied to the skin of the upper extensor part of the left arm and was covered by a 5 cm² piece of tape for 24 hours. The following comments can be made at this point: (1) from the beginning, the patch test appears as a “closed” or occlusive testing technique, (2) the size of the patch-test material was large (2.3×2.3 cm) compared to current materials, (3) the amount of ointment applied was not mentioned (the technique is therefore considered as qualitative), and (4) the duration of the application was limited to 24 hours.

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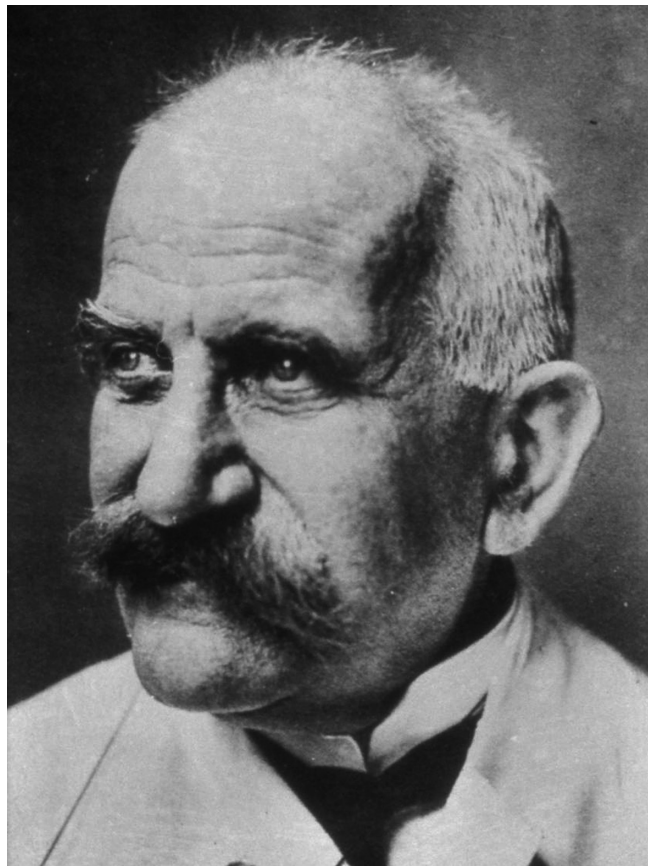


Figure 1. Professor Josef Jadassohn at Breslau University in 1926.

It should be remembered that soon after developing the patch test, Jadassohn was appointed Professor of Dermatology (1896) at the University of Bern, Switzerland, where he stayed for several years before coming back in 1917 to Breslau in his native Silesia. One of his major accomplishments there was the observation of a specific anergy in patients suffering from sarcoidosis or Hodgkin's disease.

Fortuitous Impact of the Entomologist Jean-Henri Fabre

Another description of a patch testing technique was given by the French entomologist Jean-Henri Fabre (1823–1915), who lived in Sérignan-du-Comtat, a village in Provence. This work was contemporaneous with Jadassohn's experiments; it was not designed primarily for dermatologic diagnosis but for a better knowledge of the defense mechanisms of insects.⁷ The work was inspired by the scientific approach elaborated by Claude Bernard in 1866.⁸

In 1897, Fabre reported that he had studied the effect of caterpillars on his own skin. A square of blotting paper (a

novel kind of plaster) was covered by a rubber sheet and held in place with a bandage. The blotting paper, which had previously been dipped into an extract of caterpillar hair, was folded four times so as to form a square with 1-inch sides. The impregnated paper was applied to the volar aspect of the forearm. The plaster was removed the next day. A red mark, slightly swollen and very clearly outlined, occupied the area that had been covered by the "poisoned" paper.

In these and further experiments, Fabre dissected various parts of caterpillars to isolate the noxious ones (ie, those with barbed hairs) that provoked burning or itching. Rostenberg and Solomon⁹ emphasized the importance to dermatology of Fabre's methodology, so often used in the past decades by dermatologists. For instance, many similar attempts were made during the twentieth century to isolate noxious agents (contact allergens and irritants) not only from different parts of plants, woods, and animals but also from various other naturally occurring substances and industrial products encountered in our modern environment.

Fabre's experiments are gratifying for an additional reason: they reproduce another common skin reaction of exogenous origin, contact urticaria. It is well known today that a protein, thaumetopoeitin (28 kD), is responsible for the urticarial reaction. In an attempt to reproduce Fabre's experiments, I applied caterpillars' barbed hairs to my skin, using as patch-test material a plastic square chamber (designed by Van der Bend) that was kept in place for 2 hours. After removal of the patch, two types of reactions were recorded consecutively: (1) at 20 minutes, an urticarial reaction (considered to be nonimmunologic) that faded slowly during the next 2 hours, and (2) at day 2, an eczematous reaction that spread all around the application site and was interpreted as an experimentally induced immunologic protein contact dermatitis.

Patch Testing from 1895 to 1965

Although it is difficult to assess patch testing's importance in the diagnosis of contact dermatitis between 1895 and the 1960s, the following points are clear: (1) the technique was used extensively in some European clinics and ignored in others; (2) no consensus existed concerning the material, the concentration of each allergen, the time of reading, or the reading score; and (3) the differential diagnosis between irritant contact dermatitis and allergic contact dermatitis was very often unclear.

It is no exaggeration to say that patch testers were acting like skilled craftsmen¹⁰ although—step by step—they provided new information on contact dermatitis.



Figure 2. Professor Bruno Bloch at Zurich University in 1927.

When considering this transitional period, we should recall the names of some outstanding dermatologists who directly contributed to our present knowledge and to the dissemination of the patch test throughout the world.

Bruno Bloch: An Unconditional Life Devoted to Patch Testing

Bruno Bloch (Fig 2) is considered by the international community to be one of the more prominent pioneers in the field of patch testing who continued expanding Jadassohn's clinical and experimental work. In many textbooks and articles, patch testing is often called the Jadassohn-Bloch technique.

In Basel, Switzerland, in 1911, Bloch described in detail the technique of patch testing.¹¹ The allergen should be applied to a linen strip that is placed on the back, covered with a slightly larger piece of gutta-percha and fixed in place with zinc oxide adhesive plaster; the test should then

be left for 24 hours. The size of the patch was 1 square centimeter. For the first time in the history of patch testing, the stages of skin reaction (from simple erythema to necrosis and ulceration) were graded, and Bloch stressed that a normal person and a sensitized person differ fundamentally in that only the latter reacts.

Bloch discovered and successfully synthesized primin, the specific chemical in *Primula obconica* that is responsible for allergic contact dermatitis in persons contacting that common plant.¹² He also developed the concept of cross-sensitization in contact dermatitis by studying the reactivity patterns of iodoform, a topical medication commonly used then.

Bloch described the first cases of systemic contact dermatitis, illustrated by the moulages by Lotte Volger in the collection in Zurich (Fig 3).

The idea of a standard series of allergens was also developed extensively by Bloch while in Zurich.¹³ The substances with which standard tests were made were the following: formaldehyde (1 to 5%), mercury (1% sublimate or ointment of white precipitate of mercury), turpentine, naphthalene (1%), tincture of *Arnica*, *Primula obconica* (a piece of the leaf), adhesive plaster, iodoform (powder), and quinine hydrochloride (1%).

As far as we can understand by consulting various sources of information, Bruno Bloch acted as a group leader for promoting and disseminating the idea of testing each patient with a limited standard series. This was made in close connection with Jadassohn (Bloch's teacher when he was in Bern) in Breslau, Blumenthal and Jaffé in Berlin, and (later on) Sulzberger in New York.

Poul Bonnevie and the Standard Series of Patch Tests

Poul Bonnevie (Fig 4), a former assistant of Bruno Bloch at Zurich University, was Professor of Occupational Medicine in Copenhagen. He expanded Bloch's limited standard series of tests and published it in his famous textbook of environmental dermatology.¹⁴

This list can be considered as the prototype of the standard series of patch tests. It was built on the experience gained at the Finsen Institute in Copenhagen regarding the occurrence of positive reactions to various chemicals among patch-tested patients. It is remarkable that the list was used in Copenhagen without any change from 1938 until 1955, which allowed Marcussen to publish a most impressive epidemiologic survey in 1962, concerning time fluctuations in the relative occurrence of contact allergies.¹⁵ Of the 21 allergens listed by Bonnevie, seven are



Figure 3. A unique moulage at Zurich University: clockwise from lower left, a didactic trilogy of allergic contact dermatitis from *Primula obconica*, regional dissemination (Malten's ides), and a positive patch-test reaction.

still present in the standard series of patch tests used currently: colophony, balsam of Peru, formaldehyde, potassium dichromate, nickel sulfate, p-phenylenediamine, and *Primula obconica* as is (now replaced by primin).

Marion Sulzberger and Alexander Fisher

Marion Sulzberger was one of Bloch's most brilliant assistants in Zurich and was later one of Josef Jadassohn's assistants in Breslau. In both places, he was considered a beloved American fellow worker. When Sulzberger returned to New York and became a professor of dermatology there, he modified considerably the spirit of the discipline, which was very static in the New World at that time.

However, it is acknowledged that the "master" in the field of contact dermatitis and patch testing in the United States is Alexander Fisher, through his more than 50 years of pioneering work in New York City. He has become more closely identified with this subject than has any other physician in the world. He has published countless articles describing his methodology in the search of new contact allergens and also suggesting hypoallergenic substitutes. This proved to be a useful and stimulating approach; when lecturing, he often called attention to "doing so patients are not doomed to repeated attacks." His famous book, *Contact Dermatitis*, now in its sixth edition as edited by Rietschel and Fowler,¹⁶ is an undisputed source of insight for all clinicians.

Founding of Groups of Specialists in Patch Testing

The Scandinavian Committee for Standardization of Routine Patch Testing was formed in 1962. In 1967, this committee was enlarged, resulting in the formation of the International Contact Dermatitis Research Group (ICDRG). The founding members of the ICDRG were H.J. Bandmann, C.D. Calnan, E. Cronin, S. Fregert, N. Hjorth, B. Magnusson, H.I. Maibach, K.E. Malten, C. Meneghini, V. Pirilä, and D.S. Wilkinson. The major task for its members was to standardize the patch-testing procedure (for example, the vehicles used for allergens, the concentration of each allergen, and so on) at an international level.¹⁷

Niels Hjorth (1919–1990) was the vigorous chairman of the ICDRG for more than 20 years. He organized the first international symposium on contact dermatitis at Gentofte, Denmark, in October 1975. This symposium was followed by many others, which led to an increasing interest in contact dermatitis throughout the world and to the establishment of numerous national and international contact dermatitis groups. Hjorth's contribution in promoting our knowledge of contact dermatitis was enormous; it is true to say that he ushered in a new era in environmental dermatology.

In 1980, Etain Cronin wrote an extensive book entitled *Contact Dermatitis*,¹⁸ which can be compared in its spirit to Alexander Fisher's textbook. In the meantime, in the United States, the North American Contact Dermatitis Group (NACDG) was founded, working with similar aims. Howard Maibach acted as a constant link between this group and the ICDRG.

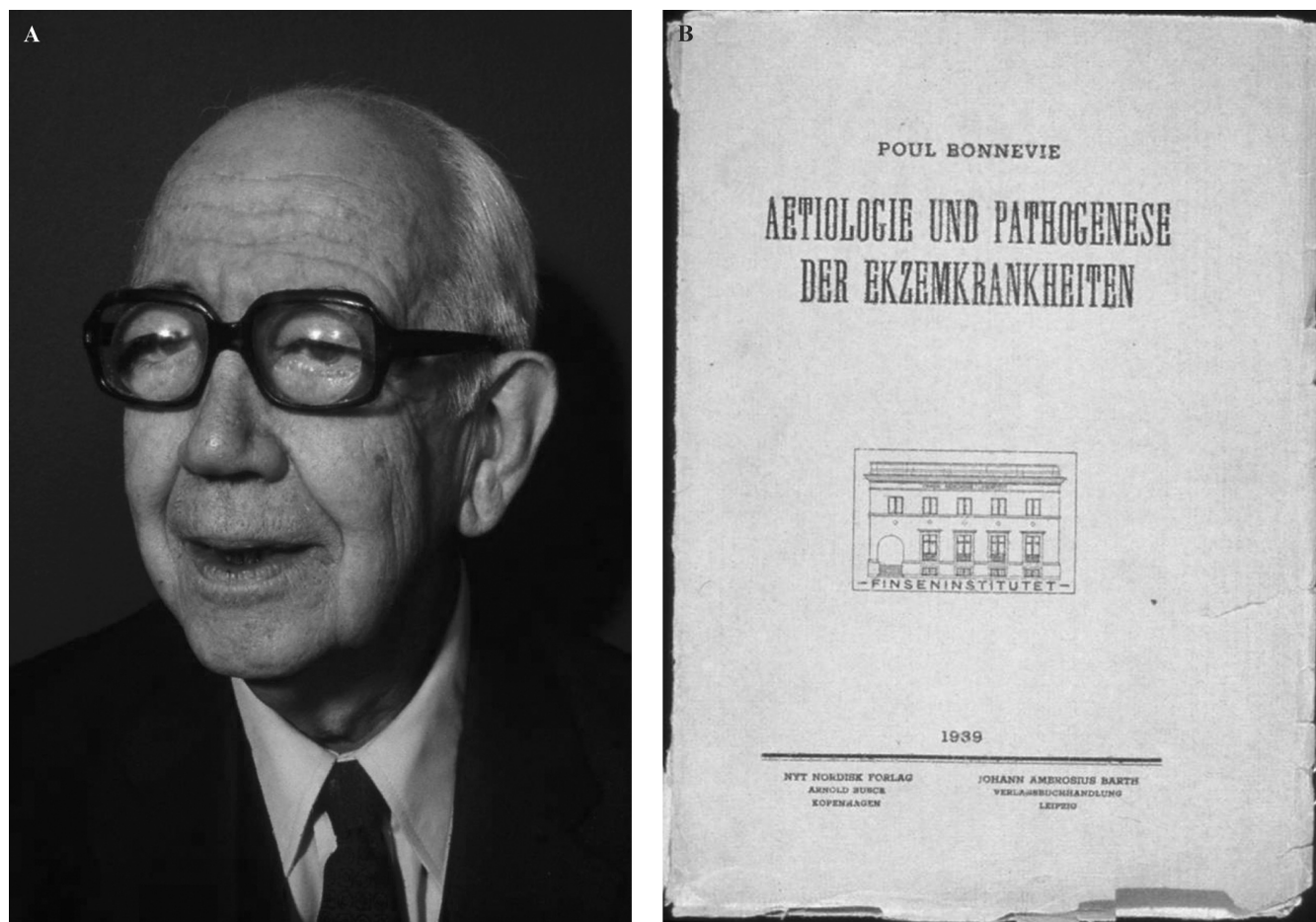


Figure 4. A, Poul Bonnevie (photograph dated 1975). B, his famous book.

Multidisciplinary Approach to Contact Dermatitis

Until the 1970s, only dermatologists had a special interest in contact dermatitis and patch testing. A real breakthrough occurred when immunologists, pharmacists, and chemists became involved in the field. First, this produced a better understanding of the mechanisms implied in contact dermatitis. Second, the developing field of dermatochemistry was an invaluable tool in the search for culprit allergens. The leader in the field was Claude Benezra in Strasbourg, France.¹⁹ After his premature and accidental death, new expansion plans were achieved by his successor, Jean-Pierre Lepoittevin.

In occupational dermatology, Fregert was also a precursor. He launched the idea of visiting factories to become acquainted with current problems, and he developed an advanced chemistry laboratory.²⁰

Recent Advances

Recent history has forwarded some new insights into reaching a better significance of patch-test results, whether positive or

negative. In case of doubt, additional tests are available. The repeated open application test (ROAT), standardized by Hannuksela and Salo²¹ and completed by other variants of use tests, provides a more accurate answer in some difficult cases.

In addition, efforts have been made to determine more precisely the relevance (or nonrelevance) of positive patch-test results,²² which is the ultimate goal in dermatoallergology.

Much attention has been paid to dose-response relationships in the elicitation of contact dermatitis, a concept that modifies our views on the matter.

A new ready-to-use patch-test system, the Thin-Layer Rapid Use Epicutaneous (T.R.U.E.) Test (Pharmacia AB, Uppsala, Sweden), was introduced in 1985 by Fischer and Maibach.²³ It represents a more sophisticated approach in the technology of patch testing, taking into account the parameter of optimal penetration and delivery of allergens through the skin. The allergens are incorporated in hydrophilic gels adapted to each individual allergen. For protection against light and air, the strips are contained in airtight and opaque aluminium pouches.

The T.R.U.E. Test represents an alternative way of patch testing,²⁴ with the intent of avoiding variations in the allergens applied to the skin.

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