
Patch Testing: A Historical and Current Perspective

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1.1 Introduction: Claude Bernard and the Birth of Experimental Medicine

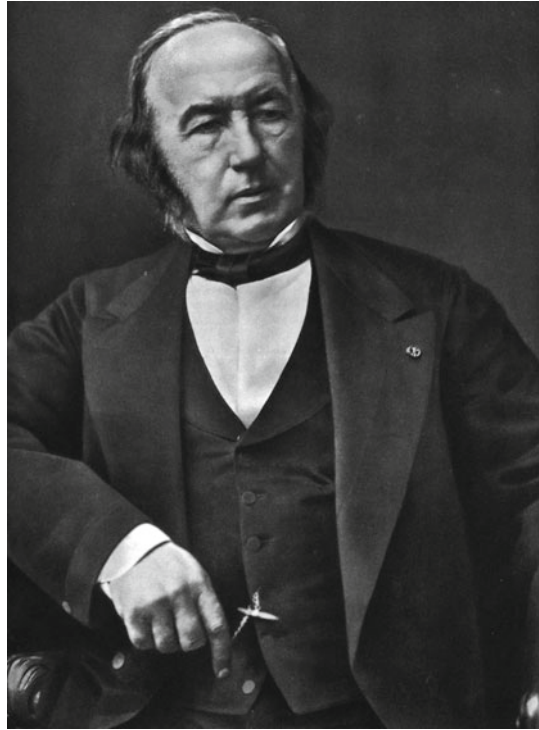
Claude Bernard (1813–1878) is universally acknowledged as the founder of experimental medicine (Fig. 1.1). His Magnum opus, written in 1865, “Introduction à l’étude de la médecine expérimentale,” was reedited in 1963 [1]. The approach includes six consecutive steps (Table 1.1): observation, hypothesis, experience, results, interpretation, and conclusion, most often abbreviated (OHERIC). Claude Bernard considered that this concise, but abridged, version was incomplete, and he added two footnotes [1]:

- We cannot give off hypotheses without having raised the problem to be solved, because a hypothesis is an answer possible for a question aroused by an observation.
- The experiment is testing the verifiable consequence of the hypothesis.

1.2 Adaptation of Claude Bernard’s Methodology to Patch Testing

In my view, when Josef Jadassohn (1863–1936) (Fig. 1.2) performed the first patch test in 1895 at Breslau (now Wrocław) University, referred to us as “Funktionelle Hautprüfung” [2], it was the very first application in dermatology of the principles of experimental medicine established by Claude Bernard [1]. The “step-by-step” strategy involved in reaching the proper conclusions is still valid today (see Table 1.1). Therefore, initially the patch test was conversely considered an “experimental” and/or a “diagnostic” tool. It has to be kept in mind that, at that time, before the advent

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Fig. 1.1 Claude Bernard**Table 1.1** The steps related to experimental medicine, after Claude Bernard, and their application to patch testing

Steps proposed by Claude Bernard as a trial in the field of experimental medicine	Application of Claude Bernard's methodology to patch testing
Observation	Onset of a skin rash
↓	↓
Hypothesis	Suspected to be either allergic or irritant contact dermatitis, or systemic contact dermatitis, or drug eruption
↓	↓
Experiment	Patch testing as a trial (or a "tool") with the hope to solve the problem
↓	↓
Results	Positive or negative patch tests
↓	↓
Interpretation	Relevance (or non relevance) of positive (or negative) patch tests
↓	↓
Conclusions i.e. « OHERIC »	Conclusions

of the concept of allergy initiated in 1906 by von Pirquet (1874–1924) (Fig. 1.3), the reproducibility of a reaction in a patient by patch testing had no real etiopathogenic meaning. In other words, there was no distinction between irritancy and allergenicity.

Fig. 1.2 Josef Jadassohn

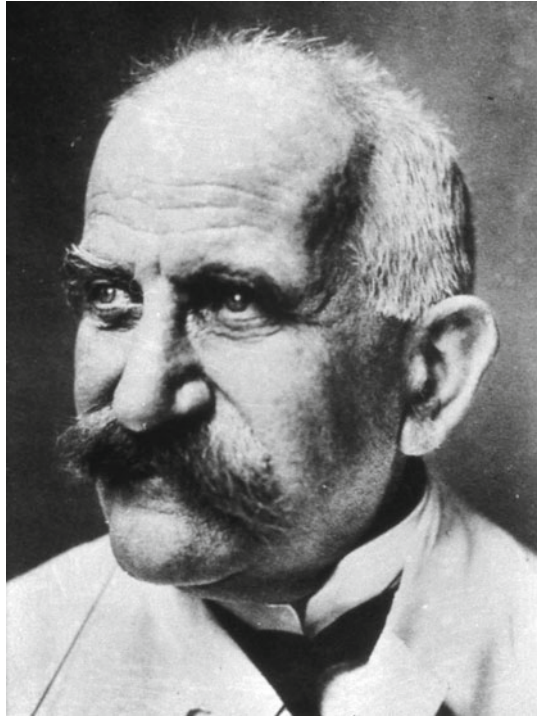


Fig. 1.3 Clemens von Pirquet

1.3 Advances from 1895 to the Creation of the International Contact Dermatitis Research Group (ICDRG)

This period has been extensively reviewed in a recent monograph [3].

A most important contribution came from Clemens von Pirquet (1874–1929), an Austrian scientist and pediatrician who noticed in 1906 that patients who had previously received injections of horse serum or smallpox vaccine had quicker, more severe reactions to a second injection. He coined the word *allergy* to describe this hypersensitivity reaction. Soon after, the observation with smallpox led von Pirquet to realize that tuberculin might lead to a similar type of reaction.

Some papers have been devoted to the scientist and his discoveries [4, 5].

Charles Mantoux (1877–1947) expanded upon von Pirquet's ideas, and the Mantoux test, in which tuberculin is injected into the skin, became a diagnostic test for tuberculosis in 1907. In the field of contact dermato-allergology, the technique of patch testing, initiated by J. Jadassohn, was extensively developed in Zurich by Bruno Bloch (1878–1933); therefore, it is sometimes called the Jadassohn-Bloch technique.

Bloch (Fig. 1.4) was an exceptional teacher and researcher. Indeed, the patch test was one of his lines of clinical research, among many others in different areas of dermatology. He suspected very early the difference between irritant and allergic contact dermatitis. He used the term “idiosyncrasy” [6, 7], which is no longer quoted nowadays; in his view, it was synonymous with allergy. Many dermatologists,



Fig. 1.4 Bruno Bloch

coming from different countries, stayed for a rather long period of time in his department; among them was Marion Sulzberger (1895–1983) [8], who disseminated and popularized the patch test throughout the United States, and also Poul Bonnevie (1907–1990), who later became Professor of Occupational Medicine in Copenhagen (Fig. 1.5). He introduced the first standard series of patch tests, vocationally oriented towards occupational dermatology [9]. Marcussen in 1962 provided a very comprehensive statistical study about the relative frequency of positive and negative patch test results of Bonnevie’s standard series [10], unchanged over the years (period of inertia potentially linked with the events of World War II). But the series had become obsolete and did not correspond anymore to the current environmental conditions.

Apart from Bloch’s flourishing school, many publications referring to contact dermatitis and patch testing were recorded in the literature from various countries, most of them of high scientific value [3, 11].

But it is clear that each “patch tester” throughout Europe and the United States had his or her own methodology; all parameters of use (allergens, concentrations, vehicles, reading time etc.) were not codified.

Moreover, it is noteworthy to recall that some individuals proficient in the field were reluctant to use systematically a “standard” or “baseline” series. In particular, Werner Jadassohn (son of Josef) in Geneva [12] and Jean Fousereau in Strasbourg [13] were strenuous opponents of the standard series; ultimately, however, they lost the battle.

It is important, in retrospect, to compare the advantages and disadvantages of a standard series (Table 1.2).

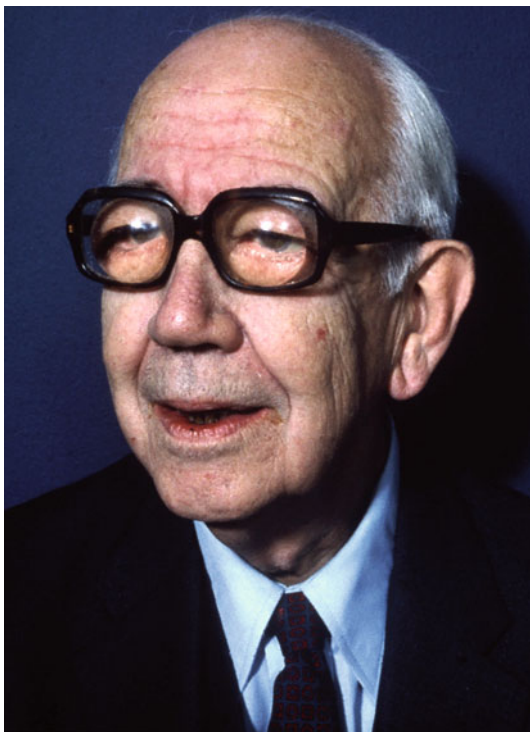


Fig. 1.5 Poul Bonnevie

Table 1.2 Advantages and disadvantages of the systematic use of a standard series

Advantages	Disadvantages [12, 13]
The standard series corresponds to an allergological check-up of each individual patient, as regards the most common allergens encountered in the environment. Positive and negative patch test results map out the allergological profile of the patient;	The standard series can produce a “sleeping” effect on the clinician’s attitude. This perverse result is avoided when the standard series is considered as a limited technical tool, representing one of the pieces of a puzzle, to be combined with other means of diagnosis. The general principle to be kept in mind is that the standard series cannot replace a detailed anamnestic (and catamnestic) investigation.
The standard series compensates for anamnestic failures. Even when the clinician tries to record carefully the history of each individual patient, he may omit important events in some cases, despite using a detailed standardized questionnaire. Positive patch test results lead the clinician to ask some additional (retrospective) questions;	Theoretically, application of the standard series could induce an active sensitization to some allergens. Common examples are <i>p</i> -phenylenediamine, primin, or isothiazolinone. The risk, however, is extremely low when testing is performed accordingly to internationally accepted guidelines.
The systematic use of the standard series permits to conduct comparative studies in different countries, thus increasing our knowledge in terms of geographic variations.	

1.4 A Revolutionary Adventure: The Founding of the International Contact Dermatitis Research Group (ICDRG)

The aim was to create a group of dermatologists from different countries, experienced in the field of contact dermato-allergology, who could share the results of their own clinical observations. The ICDRG was informally founded in 1967. Eleven members were elected and met twice a year during three full days, and the presence of everyone was compulsory. The agenda was clearly delineated before each meeting. The members of the “former” ICDRG (as we call it today) were Hans-Jürgen Bandmann (Munich-Schwabing, Germany), Charles D. Calnan (London, Great Britain), Etain Cronin (London, Great Britain), Sigfrid Fregert (Lund, Sweden), Niels Hjørth (Copenhagen, Denmark), Bertil Magnusson (Malmö, Sweden), Howard I. Maibach (San Francisco, United States), Klaus Malten (Nijmegen, the Netherlands), Carlo Meneghini (Bari, Italy), Veikko Pirilä (Helsinki, Finland), and Darrell Wilkinson (High Wycombe, Great Britain).

Niels Hjørth was the leader of the group. He acted as chairman and secretary, but this function was not official, only pragmatic. After each meeting, he wrote the minutes very carefully, without any item escaping his attention.

I was elected full member later on, after Magnusson’s sudden death.

The aims of the group were clearly defined [14].

1.5 Major Contributions of the Former ICDRG

1.5.1 Terminology

A precise definition of the terms used in contact dermato-allergy was needed and was achieved by the group [15].

1.5.2 Recommendations About the Patch Testing Methodology: The Early “Tips” in Contact Dermato-Allergy

After long discussions at the biannual meetings, several rules were decided and promulgated. The main recommendations are presented in Table 1.3. For more detailed information, see reference [16].

Table 1.3 Recommendations of the (former) ICDRG related to the patch testing methodology [16]

Choice of a vehicle for the allergens being applied onto the skin	After long discussions, petrolatum was considered the best compromise, because it allows good penetration of the allergens and warrants a long-dated preservation of most allergens kept in the fridge The chemical incompatibility between some allergens and petrolatum was pointed out (e.g., formaldehyde, to be dissolved in water) The use of organic solvents was abandoned due to their irritant properties
Choice of the site of application	The upper back was considered the best site for the application of the patch tests, in terms of reliability and effectiveness. The decision was based upon earlier experiments conducted by Magnusson et al. [17, 18]
Reading time	A consensus was reached to obtain the most accurate results: two readings (at 48 and 96 h) were ideal, but if only one could be achieved, the advisable reading time was 72 h. A third reading at 7 days was strongly recommended, to reveal positive reactions to either slow-reacting allergens (i.e., neomycin, corticosteroids, etc.) or in the case of “late reactors.” It was advocated that one single reading at 48 h had to be banished [16]
Scoring patch test results	The scoring codes of the ICDRG [15] have been universally acknowledged and quoted in many papers An update of this scoring index is potentially on the way
Repeating the test when doubtful ($\pm?$) results do occur	Questionable patch test results ($\pm?$ or even + for some allergens) were of concern for the committee Repeating patch tests was a judicious step proposed by the group. Allergens were tested at lower concentrations to reach a more precise distinction between irritant and allergic reactions
The standard (baseline) series: the main task of the “former” ICDRG	Due to its undeniable advantages, creating an updated standard series of allergens was a real priority. Collecting the results of their individual clinics, the ICDRG members decided that the choice of the list (20 allergens) was dictated by the 1 % rate (i.e., the general approximate cutoff with 1 % positives in an eczema population in a massive screening) It is considered nowadays interesting but outdated Additional series were also designed

Table 1.4 Items that were incompletely covered by the (former) ICDRG*1. Patch test materials*

No instructions were precisely given by the members, as far as the patch test material was concerned. Some used the non-chamber AI-test, whereas others privileged the Finn Chamber. No constraint, but therefore the comparative joint studies were partially biased

2. The amount of allergen applied to the skin

In relation to item 1, the amount of allergen applied onto the skin was of no concern, but we have to consider that it was 40 years ago!

3. The relevance of positive patch tests

The problem was considered, but members thought that it was difficult to define it precisely, and they did not publish about it. They considered that a complete dermatological “checkup” of the patients was the only way to solve the problem. Anamnestic and catamnestic data, a time-consuming procedure, were in most cases contributory

Table 1.5 Some recommendations of the “new” ICDRG

The repeated open application test (ROAT)	Introduced by Hannuksela and Salo [19], it is an invaluable additional tool of investigation, complementary to the patch test [20, 21]
Revised minimal baseline series	Some papers have been written, referring to the “minimal” baseline series, intended to be used worldwide [22, 23]
Relevance of positive and/or negative patch tests	The problem of the relevance (or non-relevance) of positive and/or negative patch tests is still a difficult issue. Some trails have been traced to help the clinician [24, 25]

1.5.3 Some Items That Were Not Studied Thoroughly by the (Former) ICDRG

Some areas of investigation were incompletely covered at that time. They are listed in Table 1.4.

1.5.4 The Retirement of Members of the “Former” ICDRG and the Revival of the Group

When most of the members retired, some of them advised the dissolution of the group, since they considered that such an adventure was unique and could not be repeated as such. Nevertheless, Howard Maibach decided to take up the challenge, and the revival was a success. At that time, Matti Hannuksela joined the group and developed the repeated open application test (ROAT) [19]. Some of the activities are summarized in Table 1.5.

The list of the current members is presented in [ICDRG members](#).

Table 1.6 The main “tips” from the EECDRG and the ESCD

Appropriate amounts of petrolatum and/or liquids to be applied at patch testing	This is a major contribution for the standardization of patch testing, to be adapted to Finn and/or plastic chambers [26, 27]
Sequential retesting when in doubt of the occurrence of the excited skin syndrome (ESS) in a patient	Development of strategies to solve the problem of EES was considered of primary importance in the patch test readings [28–30]
The allergen bank	An innovative approach, initiated in Odense (Denmark), providing extra-allergens, not distributed in the market, to practicing dermatologists [31, 32]
Reliability of patch testing in drug eruptions	It is a domain that exploded in the last few years. The indications and limitations of patch testing have been progressively pinpointed [33–36]
Ultrasonic bath extracts technology	A very useful tool for extracting allergens from patient-supplied products/materials [37]
Semi-open (or semiocclusive) tests	A very important step in the investigation of difficult cases (patient-supplied products). Halfway between the patch test and the ROAT test [38, 39]
Further advancements in the methodology of the ROAT test	Improvements related to the reliability of the ROAT test: investigations about the site, the size of the test, and the scale of evaluation [20, 21, 40]

1.5.5 The European Environmental and Contact Dermatitis Research Group and the European Society of Contact Dermatitis

In the meantime, contact dermato-allergology, the patch testing procedure, and its additional tools of investigation flourished throughout Europe.

The foundation of the European Environmental and Contact Dermatitis Research Group (EECDRG) and soon after of the European Society of Contact Dermatitis (ESCD) played an important role in these continuous improvements. Moreover, the ESCD decided to create various working subgroups, trying to increase our knowledge about pending problems and to help the clinician in his or her practice. For example, one of the important topics was to evaluate the reliability of patch testing in drug eruptions, among many others. The continual updates in the field were presented in specific sessions during the Congresses organized by the ESCD and published in *Contact Dermatitis*. By the way, some members of the “new” ICDRG were and/or are members either of the EECDRG or of the ESCD. It is noteworthy that many of the “tips” presented in this monograph have been developed either by the EECDRG or the ESCD (Table 1.6).

The aim of the ICDRG is to disseminate these advances all around the world.

1.5.6 Another Adventure: The TRUE Test

Torkel Fischer and Howard Maibach [41, 42] developed the TRUE Test, a well-known technology of patch testing, as a joint venture with Pharmacia (Uppsala, Sweden) at first and with SmartPractice (Phoenix, Arizona) later on.

A detailed overview of the TRUE Test is presented in our previous book [43].

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