**HISTORICAL PAGE**

# THE HISTORICAL BACKGROUND OF ALLERGIC RHINOPATHY THERAPY

The therapy of the tiresome symptoms marking allergic rhinopathy already begins at the dawn of medicine's history. For centuries empirical attempts at treatment have been tried out in succession, having recourse to the most heterogeneous substances!

These attempts were multiplied in the course of many centuries, but it was only in the 19th century and at the beginning of the 20th century – coinciding with the appearance of new aetiological theories – that the therapy becomes more and more targeted and effective. This was a slow process which took place within a timeframe of somewhat over 100 years, from the time Elliotson (1888) first ascribed them to pollens up to the discovery of the properties of cortisone in 1948. The affirmation of Elliotson's theory impelled the experts to explore methods to prevent pollens from coming into contact with the nasal mucosa, and thus filters were proposed consisting of pouches made of silk or rubber, filled with cotton wool (Woodward, 1888), pads impregnated with phenolated or camphorated glycerine (Woodward, 1888), or else glass platelets introduced into the nasal fossae (Hannay, 1881).

Towards the end of the 19th century a local therapy was also favoured, which – at least initially – seemed to achieve excellent results in eliminating the symptoms of nasal irritation, namely anaesthetisation by means of cocaine. This started in 1884 thanks to the Viennese school and, in particular, Edmund Jelinek who applied it to the pharynx and larynx, and Leopold Koenigstein and Carl Koeller, who used it opthalmologically. Whilst cocaine was originally applied endonasally by the Austrian Carl Stoerk, and the American Frank H. Bosworth who in the same year used it first as an anaesthetic for galvanocaustic crises and later as a local therapy for checking hyperreactive crises (Stoerk, 1884). Bosworth considered cocaine an easily managed drug without secondary effects on the nasal mucosa. However, this excessive faith was short-lived and in fact in 1886 already Seth Scott Bishop prudently alerted the colleagues to the secondary effects on the nasal mucosa. Repeated cocaine applications to the nasal mucosa, which were carried out by sustainers of the theory of reflex neurosis, of course, exposed patients to the risk of medicamentous rhinopathy with vasoparalysis and consequent constant congestion of the turbinates, with even greater discomfort to the patient than the one caused by the initial illness. Rightfully so, Solis-Cohen (1898) pointed out that "the excessive use of the drug in the nose is followed by a reaction, probably due to a local paresis of the vessels, which is much more disagreeable than the original symptoms".

These side-effects were the same as those noted later with vasoconstrictors. Their use for hay fever would be introduced towards the end of the 19th century, in 1885, with a preparation for local use based on suprarenal extracts, Rhinokulin. Suprarenal extracts in hydroglycerin solution were used by Solis-Cohen himself. He noted that vasoconstriction resulted into a satisfactory decongestion, apparently "without the disadvantages of cocaine, in complete safety, without toxic secondary effects or tiresome sequelae. Unfortunately, the disadvantages due to abuse of local vasoconstrictors would not be discovered until a long time after.

In fact, all these kinds of therapies proved to be mere palliatives, incapable of providing a persistent effect and following the initial enthusiasm, a deeply rooted pessimism spread among clinicians on account of the impossibility of disposing of a drug capable of preventing crises or of interrupting them once initiated. This is clearly shown by the words of one of the more authoritative 19th century experts in this field George M. Beard (1876): "…nothing can be done to prevent the attacks … all medical treatment during the attack is useless or worse than useless, no means of relief having yet been discovered….".

A revolution in the therapy of vasomotor rhinopathy was observed at the beginning of the 20th century thanks to the research of Philipps Dunbar of the Institute of Hygiene, Hamburg, who maintained that pollen, or rather a toxic fraction of the latter, Pollentoxin, was responsible for the crises of asthma or rhinitis caused by *Graminaceae* and that, in agreement with the theories on anti-infectious vaccination, it was necessary to institute a desensitising therapy (Dunbar, 1903). Accordingly, he isolated a pollinic toxoalbumin and prepared an antitoxin, Pollantin, which was soon used in therapy, but which as a result of the frequent undesired reactions, was abandoned by many. Nevertheless, Pollantin continued to be used for a long time; indeed, it was still advocated in medical texts in the 1930s. The original nature and importance of Dunbar's discovery, which was to open the road to the desensitising therapy of allergies, was quickly recognised by the international scientific community and among the many positive judgements we would recall the one by Sir Felix Semon (1903), a man usually parsimonious of praise of his colleagues ("… there cannot be any doubt that Professor Dunbar has made a very interesting and important discovery …").

Shortly afterwards, one of Dunbar's pupils, Wolfgang Weichardt (1905) brought out a polyvalent vaccine preparation, Graminol, which had the purpose of immunising against hay fever by means of progressive doses of subcutaneous injections, according to Besredka's experiments; while the endonasal application of a vaccine prepared with extracts of pollens and plant dusts was elaborated for the first time in 1907 by G. Billard and C. Maltet.

Specific desensitising therapy of pollenosis was once more taken up in 1911 by Noon and Freeman, in 1919 by Walker, in 1920 by Mignon and in 1921 by Pasteur Vallery-Radot. Another form of prophylaxis was to explore the means of preventing contact with sensitising substances by setting up isloated rooms into which filtered air was to be introduced. These rooms enjoyed a certain success in the course of the 1920s, although they had been foreseen from as far back as 1873 by Blackley. Their realisation, however, dates back to 1924 thanks to William Scheppergrell in the USA and the Dutch clinician Wilhelm Storm van Leeuwen (1929), who set up a "Klimakammer" in Leyden, complete with appropriate water filters. These would be used two years later in Cleveland by Bronath Cohen (1926), while other systems of filtering including electrostatic filters would be perfected between 1926 and 1936 by Otto Voss, K. Griebel, G.N. Jack and L.H. Grieg (Schadewaldt, 1983). However, in the first years of the 20$^{th}$ century cocainisation either or not in combination with vasconstrictors continued to be used for hyperreactive rhinopathies. As far as vasoconstrictors are concerned, we may recall that suprarenal extracts were gradually replaced in local therapy by their active principle, adrenaline, isolated in 1901 by Jockichi Takaminc (1901) used at a concentration of 1 to 1,000 providing an adequate decongestant effect as well as less irritant consequences. Once use of cocaine had been abandoned, adrenaline alone continued to be used, until it was replaced by synthetic ephedrine introduced into the therapy of rhinology by T. Grier Miller in 1925: "Locally applied to the nasal mucous membrane, ephedrine causes prompt contractions of the vessels which persists for more than three hours and has no local irritant effects". In 1927 ehpedrine was coupled with another synthetic product, ephetonin, and its use was protracted for a long time until both were replaced by privine or napthazoline, synthesised in 1941 (Schadewaldt, 1983).

Other ways of treatment were proposed in the course of this century, such as the ones used in France and Great Britain which used peptones per os in an attempt to achieve a desensitisation (Auld, 1921) or autoserotherapy introduced by George Dhers in 1922 and perfected in 1934 by A. Jacquelin and G. Bonnet with series of intramucous infiltrations of autoserum in the lower turbinate.

Physical therapy too enjoyed its moment of favour: in 1921 S. Gillet proposed for asthmatics total body irradiations of short duration, while for allergic rhinitis F.E. Haag (1931) advised nasal roentgenotherapy.

But the progress in anti-allergic therapy in the 20$^{th}$ century is without a shadow of doubt significantly characterised by the discovery and introduction of antihistaminics and of cortisone.

The development of the first antihistaminics can be largely attributed to Daniel Bovet, who from the beginning of the 1920s onwards devoted himself to research on the action of histamine, thereafter taking up these studies in the Department of Chemical Therapy of the Pasteur Institute in Paris, at that time directed by Fourneau. His studies were above all directed to histamine antagonists, as yet quite unknown. In 1937, in collaboration with Anne Marie Staub, by means of studying the homologues of peroxan (an adrenergic blocker, discovered a few years earlier by Fourneau, Bovet found out that one of these, compound 929F, had the property of protecting animals from lethal doses of histamine, and that the same was true for other similar compounds (Bovet and Staub, 1937). This discovery had immense implications, however, tests on human beings were prevented, because of the high toxicity of these substances. Several years had to elapse before it was possible to achieve an effective and easily manageable anti-histaminic, until finally in 1942 antergan (phenbenzamine) was achieved. This was synthesised by Mosnier and from the biological point of view was studied by Bovet himself and by B.N. Halpern who shortly afterwards introduced into therapy two further even more active and safer antihistaminics: neo antergan (mepyramine) and fangergan (promethazine), which gave rise to a long series of synthetic compounds which succeeded one another in the therapy of allergopathies (Sterpellone, 1992).

The history of the discovery of cortisone in its initial phases is surrounded by a certain melodramatic halo. In fact just before World War II the emissaries of Hitler's "Reich" concluded negotiations with the Argentinean cattle breeders whereby they would take over all the suprarenal glands of the animals butchered. This fact aroused the suspicions of the Allied Secret Services, which, in the absence of other clues, supposed in a certain flight of imagination, that particular substances could be extracted from the suprarenal glands capable of enhancing the performance of the "Luftwaffe" pilots. The task of ascertaining what this substance could be was entrusted to one of the most well-known researchers working for the US Government, Edward Calvin Kendall, the discoverer of thyroxin and future Nobel prize winner, who at that time was studying precisely the activity of the suprarenal glands. He had discovered that a substance (compound E or cortisone) contained in the extract of suprarenal cortex had the particular property of preventing experimental hyposuprarenalisms (Kendall et al., 1934); shortly afterwards scientists in Europe too arrived at similar results (Wintersteiner and Pfiffner, 1936).

Nevertheless, Kendall's studies had practically come to a standstill for lack of funds, which on the contrary arrived in large quantities and unexpectedly from the Pentagon in the war years, enabling it to carry out on 21$^{st}$ September, 1948, the first human experiment, on a patient suffering from rheumatoid arthritis, with truly miraculous results (Hench et al., 1949). These results were later redimensioned by the observation of the side-effects for which remedies were sought after 1952, the year in which Robert Woodward obtained synthetic cortisone (Woodward et al., 1952) bringing out more and more manageable compounds, but still provided with an intense antiphlogistic and, consequently, also an anti-allergic property.

REFERENCES

1. Auld AG (1921) The use of the peptone in asthma and its congeners. Br Med J 1: 696
2. Beard GM (1876) Hay-Fever or Summer Catarrh, its nature and treatrnent. New York, p. 4

3. Billard G, Maltet L (1907) Sérothérapie contre le rhûme des foins et l'asthme. J Physiol Path Gén 9: 309
4. Bishop SS (1886, 1887) Cocaine in hay-fever. JAMA 6: 141; 7: 44
5. Blackley CH (1880) Hay-fever its causes, treatment and effective prevention. Londra, p. 255
6. Blackley CH (1881) On the treatment and prevention of hay-fever. Lancet 2: 371
7. Bosworth FH (1889) A treatise on diseases of the nose and throat. New York, p. 229
8. Bovet D, Staub A (1937) Action protectrice des éthers phénoliques au cours de l'intoxication histaminique CR Soc Biol 124: 547
9. Cohen MB (1926) A pollen filter: preliminary report of hay-fever in rooms made pollen free by new filter. Med J Rec 123: 322
10. Dhers G (1922) La rhinite spasmodique apériodique et son traitment par l'autosérotherapie désensibilisatrice. Parigi
11. Dunbar WP (1903) Ätiologie und specifische Therapie des Heufieber. Münch Med Wschr 50: 924
12. E1liotson J (1833) Catarriius aestivus or Hay-Fever. Lond Med Gaz 12: 164
13. Freeman J (1911) Further observations on the treatment of hay-fever by hypodermic inoculation of pollen vaccine. Lancet 2: 814
14. Haag FE, Schreuss H (1931) Über die Röntgenbehandlung des Heufieber: Strahlentherap 42: 485
15. Hannay JB (1881) Prevention of Hay-Fever. Br Med J 2: 872
16. Hench PS, Kendall BC, Slocumb CH, Polley HF (1949) The effect of a hormone of the adrenal cortex (17 hydroxy-11 dehydrocortisone: compound E) and of a pituitary adrenocorticotropic hormone on rheumatoid arthritis. Proc Mayo Clin 24: 181
17. Jacquelin A, Bonnet G (1934) Presse Méd 14: 2
18. Kendall EC, Mason HL, McKenzie BF, Myers CS, Koelsche A (1934) Isolation in cristalline form of the hormone essential to life from the suprarenal cortex, its chemical nature and physiological properties. Proc Mayo Clin 9: 245
19. Mignon M (1920) Considération sur le traitment antianaphylactique de la rhinite spasmodique. Rev Laryng Paris 41: 475
20. Miller TG (1925) A consideration of the clinical value of Ephedrin. Am J Med Sci, 170: 157
21. Noon L (1911) Prophylactic inoculation against hay-fever. Lancet 1: 1572
22. Pasteur VaIlery-Radot JL, Hagueneau J, Watelet A (1921) Origine anaphylactique de certains crises d'hydrorrhèe nasale. Traitment antianaphylactique. Presse Méd 29: 764
23. Reichstein T (1938) Über Bestandteile der Nabennieren-Rinde. VI Trennungsmethoden sowie Isolierung der Substanzen H. Helv Chem Acta 19: 1107
24. Schadewaldt H ( 1983) Geschichte der Allergie, Muenchen
25. Schadewaldt H cit II, p.327
26. Schadewaldt H cit II: 182; III: 26
27. Scheppegrell W (1922) Hay-Fever and Asthma, cause, prevention and treatment. Philadelphia
28. Semon F (1903) Some experiments on the nature and specific treatment of Hay-Fever. Br Med J 1: 713
29. Solis-Cohen S (1898) A preliminary note on the treatment of hay-fever with suprarenal. Philadelphia Med J 2: 341
30. Sterpellone L (1992) Asma bronchiale. Una Storia. La Spezia, p.129
31. Stoerk C (1884) Ueber die Anwendung des Cocain in der Laryngologie und Rhinologie. Wien, Med Blätter 51: 6
32. Storm van Leeuwen W, Tissot van Patot PN (1929) Allergenfreie Kammern in Privatwohnungen. Klin Wschr 8: 986
33. Takaminc J (1901) Adrenalin, the active principle of the suprarenal glands and its mode of preparation. Am J Pharmac 73: 523
34. Walker IC (1919) Sensitization and treatment of bronchial asthmatics with pollens. Am J Med Sci 157: 409
35. Weichardt W (1905) Über specifisches Heufieber serum. S Ber Phys, Med Soc Erlangen 37: 209
36. Wintersteiner OP, Pfiffier JJ (1936) Chemical studies on the adrenal cortex. J Biol Chem 111: 599
37. Woodward R (1888) New oro-nasale inhalers and Hay-Asthma. Br Med J 2: 213
38. Woodward RB, Sondheimer F, Taub D, Heusler K, McLamore WM (1952) The total synthesis of steroids. J Am Chem Soc 74: 4223


D. Passàli, G. Sperati