CHAPTER 1

Urticaria: Historical Aspects

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We are for the most part ignorant about the causes of chronic urticaria

—Ferdinand Hebra (1816–1880)

INTRODUCTION

History of medical science is fascinating. The cause of some of the very common symptom and sign has remained under the veil of enigma and has attracted and deceived the most towering personalities of the medical history when they engaged themselves in the search of their aetiology. The urticaria of various forms and figures (Fig. 1.1) is one of such vexing problem which is known since the early days of medical history, yet has remained in large part an unsolved mystery regarding its cause and many other aspects.

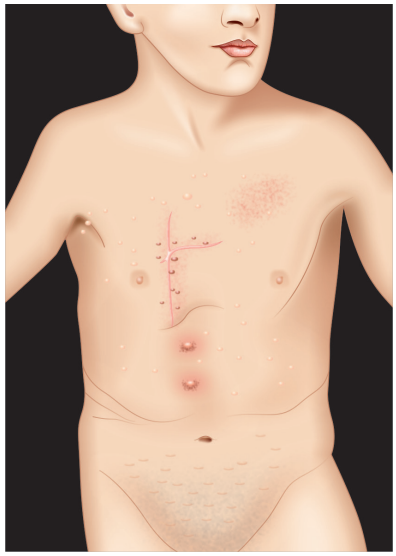

Fig. 1.1: 'The trunk of a young man with a wheal caused by urticaria' by HMT Hill (1894). (*Credit:* Wellcome Collection. Creative Commons Attribution (CC BY 4.0). https://creativecommons.org/licenses/by/4.0)

What is there in a name?

Since the early days, urticaria has assumed various names—some are right and others are wrong from the nosological point of view. Hippocrates (*c.*BC 460–370) recognised urticaria as a distinct entity (Henz BM, 1998). Celsus (*c.*BC 30–AD 45) described it in the sixth book of his "*De Medicina*" as *aspritudo*. Plinius (*c.* 1st century) termed it as *uredo*. In 10th century, Hali Ben Abbas coined the term *essera* which stands for elevation (Czarnetzki BM, 1996). Lieutaud (1703–1780) termed it *porcellana* and Sauvages in 1783 called it *scarletina urticata*. Zedler called the entity as *urtcatio* in 18th century. Probably, it was Johann Peter Frank (1745–1821) who first to use the term *urticaria* in 1792, though the other opinions advocated that the term was first used in Encyclopaedia Britannica in 1771. Alibert used the term *cnidosis* in 1833 and it was in vogue even in the later part of the 19th century.

Entirely different etiologic entities like papular urticaria and urticaria pigmentosa had been clubbed at times with urticaria (Warin RP et al. 1974).

Earliest Records

The earliest records clearly mentioned that this entity can be traced back to BC 200 when one found the term *Feng Yin Zheng* in the Chinese treatise *Huangdi Neijing* written during the Han period (Maurer M, 2014). In India, the mention of such an entity is available in *Brihat Trayee* (*c.*BC 6th century–AD 2nd century) as *Kotha* and also as *udarda*, *sheetapitta* in the famous *Madhava nidanam* of the later period (*c.* 7th century AD) (Sason R et al. 2014). In Western literature, Hippocrates, Plilinius, Celsus and others described the entity in the pre- and early Christian era.

Aetiology of Urticaria—a Never Ending Dispute

Since the early days of the medical history, it had remained a challenge to the medical researchers and clinicians to find out the real reason of this common problem with an aim of establishing a plausible treatment methodology to ally the suffering of the patients. The search had led to relate innumerable conditions that stretched from meteorological constellation to mental stress, food to sexuality and so on. In early Indian Ayurvedic texts, the aetiology was ascribed to the *Satmya-Asatmya* concept arising from improper food and various poisonous materials (allergens) (Sason R et al. 2014). In traditional Chinese Medicine, wind is held responsible as the major pathogenic factor for this problem. Hippocrates told about the contact urticaria from nettles and also described the role of gastrointestinal system in the causation of this disease (Maurer M, 2014). Zakaria Razi (AD 850–923), the famous Persian physician, thought abnormal functioning of the biles as responsible factor (Zakaria AMBZ, 1994). Thus various concepts were there to explain the aetiology, though none was able to give a satisfactory answer. Till the 17th and 18th centuries almost all arguments were revolving around one or other reason affecting the humoral theory, and the confusion regarding a standard nature of the disease also persisted. Sydenham (1624–1689) classified urticaria with erysipelas. Another towering figure of that era, Lorry (1726–1783) clubbed it with prurigo. Vogel (1724–1774) was the first to separate urticaria from other entities like scarlatina and erysipelas. In 16th century, for the first time, a causal relation was described between urticaria and intake of food protein (Czarnetzki BM). Morgagni (1682–1771) published his postmortem study and argued that affection of a single organ can lead to widespread manifestation. Austrac (1684–1766) considered urticaria as a result of obstruction leading to local oedema. Other than these, different other theories like Idiosyncratic theory (Behrens, 1700), Humoral theory (Chemniz, 1703), Theory of sympathies (2nd half, 18th century), Toxin theory (Chalmers, 1776), Nervous theory (Eulenburg, 1867), Meteorological theory (Frank, 1823), Menstrual theory (Mosler, 1864 Microthrombosis theory (Philipson, 1899). Theory of inflammation (Torok, 1903) and Allergic theory (Joltrain, 1930) were advocated between 18th and 20th centuries (Czarnetzki BM, 1986). With the passage of time, more scientific and logical thinking were evolving which in later years gradually replaced the empiricism by scientific views. In the mid-19th century, there were a number of theories that involved various factors but almost all of them had a common opinion the something 'idiosyncratic' factor must be playing a significant role. Bazin (1807–1878), the most famous French dermatologist, related urticaria with systemic disorders. Trosseau (1801–1867) told about similarity between asthma and urticaria. Hebra (1816–1880), another prominent personality, argued about the role of emotion, food, drugs, intestinal worms, disorders of the female sexual organs, etc. Auspitz (1835–1886) hold

tonicity of the blood vessels as a reason. Some other authorities like Schwimmer, Anderson, Drysdale put forwarded many theories involving neurosis and psychological aspects (Warin RP et al. 1974).

The whole scenario took a new turn with the description of mast cells by Paul Ehrlich (Fig. 1.2) in his doctoral thesis in 1877 (Ehrlich P, 1877). After a long period of about seven decades, Riley and West were the first to show that mast cells were the principal source of histamine. Histamine was already extracted and described by Dale in 1906. Dale was famous for the 'Dale criteria' that had to be fulfilled by a substance that could claim to be responsible as a mediator of inflammation (Dale HH, 1906). The next milestone was the description of importance of histamine by Lewis in 1927. His famous *triple response* gave a much clear view about the mechanism of urticarial wheal formation (Lewis T, 1927). Subsequent discovery of two subsets of histamine receptors—H_1 and H_2 led to further enlightment. Very recent discovery of H_4 receptor and its antagonist's role in uriticaria have attracted attention (Fung-Leung W-P, 2004). The discovery of immunoglobulin IgE by Ishizaka in 1966 explained the mechanism of acute allegic urticaria in a better way which corroborated with the Gell and Coombs type I reaction pattern (Ishizaka K et al. 1966). The further endeavour to explain the causation of the urticaria came from authorities like Juhlin, Doeglas, Warners and others who propounded the theory of food additives and various food colouring materials as the contributory factors (Michaelsson G et al. 1973). In 1980s, the next suspect was the affection of *Helicobacter pylori* (Burova GP et al. 1998). In recent years, the role of antibodies and autoimmunity have come into play. Grattan in 1986 has shown that in some patients the serum (of same person), if injected intracutaneously, may lead to the wheal formation. This provides a strong support towards some vasoactive factor circulating in the blood (Rorsman H et al. 1962). Recent researches on mast cell biology have attracted attention towards MRGPRX2, a new member of the Mas-related G protein-coupled subfamily of receptors (MRGPRS), in the causation of various allergic conditions including chronic spontaneous urticaria (Quan PL et al. 2021).

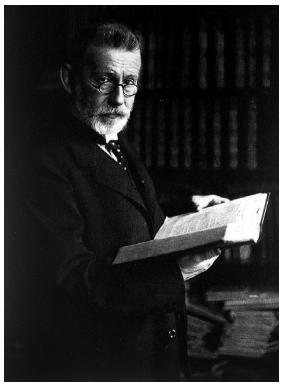

Fig. 1.2: 'Portrait of P Ehrlich in his study' by Alfred Krauth, Photographische Gesellschaft, Berlin, 1910. (*Credit:* Wellcome Collection. Creative Commons Attribution (CC BY 4.0) https://creativecommons.org/licenses/by/4.0)

In this period of SARS–Covid pandemic, urticaria has been reported as one of the most common cutaneous manifestations suggesting the role of either the virus itself or the immunological response arising out of the infection (Seque CA et al. 2022; Do MH et al. 2021).

Thus, the journey that started from a hazy picture of the role of food to psychological affection has travelled a long way to develop into a clearer portrait … but not complete yet. Many questions are yet to be answered.

Urticaria

Urticaria is not just a single and uniform entity. It has various forms and these may vary according to aetiology, morphology, etc. Cholinergic urticaria was first described by Duke in 1924 (Duke WW, 1924). Shelly and Rawnsley in 1964 described aquagenic urticaria in three patients (Shelly WB et al.

1964). Familial cold urticaria was described by Kile and Rusk in 1940 (Kile RL et al. 1940). Duke described an interesting case of direct heat urticaria (Duke WW, 1926). In this way, various varieties have been described and still the process is going on.

Angioedema—an Entity of Special Status

Angioedema is a common associated phenomenon in urticaria. It was known in medical science since long. In 1586, Marcello Donati (1538–1607) first gave lip swelling in response to ingestion of egg. Robert Graves (1796–1843) told about acute circumscribed urticaria. It was Eugen Dinkelacker and his teacher Quincke who described the condition in detail. Felix Mendel in 1902 first associated the name of Quincke with the angioedema but Bannister of Chicago citing earlier reports of the condition disagreed with the term Quincke's oedema. The term angioneurotic oedema was first used by Paul Strübing (1852–1913) in 1885 (Mukhopadhyay AK, 2019). Hereditary angioedema was described by Oslar in 1885 (Oslar W, 1888). Virginia Donaldson and Richard Evans identified the biochemical defect in the C1-estarase deficiency in hereditary angioedema in 1963 (Donaldson VH et al. 1963).

Historical Aspect of Management

In ancient Indian medicine, management of urticaria was mentioned in *Charaka Samhita*, *Susruta Samhita*, *Bhavprakash*, *Chakradutta* and other important texts. They mentioned about alteration and restriction of certain foods and prescription of some medicines like *Udarda prashaman mahakashaya, Katu Taila, Navakarshika guggulu*, etc. (Maurer M, 2014). In Arabian medicine, the treatment of urticaria with liniment was mentioned by Rabban Tabri (810–895) (Tabri AR, 2010). Heberden (1710–1801) recommended bland cooling topical application as the management. Other than this, the treatment were centred around the cause believed to be responsible by the concerned physician. The whole scenario changed with the discovery of antihistaminic drugs. Daniel Bovet and Anne-Marie Staub first described antihistaminic agent in 1937 (Staub A et al. 1937). Daniel Bovet (Fig. 1.3) received Nobel Prize in 1957 for his work on the development of antihistamine. Adrenaline was developed in 1901 and found its application in the management of anaphylaxis in the year 1912. The first clinical antihistamine drug was phenbenzamine (2339RP) (Sardana K et al. 2016). It was introduced by Bernard Halpren for clinical

Table 1.1: The timeline

c.BC 6th century–c.AD 2nd Century	Ayurvedic treatises (*Charaka Samhita*, *Susruta Samhita*, etc.) mentioned *Kota*, *Sheetapitta*, etc. may be similar to urticaria.
c.BC 200	Huang Dineijing mentioned Feng Yin Zheng
AD 1586	Donate described angioedema
AD 1792	Johann Peter Frank (1745–1821) was the first to use the term urticaria
AD 1877	Paul Ehrlich told about the mast cells
AD1906	Henry Dale described histamine
AD1927	Lewis described 'Triple response'
AD1937	Bovet and Staub told about antihistaminic agents
AD 1942	Phenbenzamine, the first antihistamine introduced for clinical use
AD 1981	Second generation antihistamine introduced
AD 2014	Omalizumab was approved by US FDA for the management of chronic idiopathic urticaria.

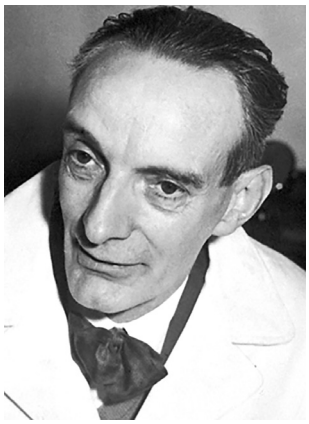

Fig. 1.3: Daniel Bovet (1907–1992) (*Source:* http://www.nobelprize.org/nobel_prizes/medicine/laureates/1957/. Credit: Unknown author, Public domain, via Wikimedia Commons)

use in 1942. The first clinically useful synthetic antihistaminic agent was mepyramine. Diphenhydramine hydrochloride was the first agent that underwent formal investigative study in North America (Greaves MW, 2007). The second generation antihistaminics were introduced in 1981 (Simon FER). Though a lot of pharmacological agents have been in use for the management of the urticaria, the introduction of biologics is a new addition in the history of urticarial management. Among various biologics, Omalizumab got approval from the US FDA in 2014 for the treatment of chronic idiopathic urticaria (Sánchez-Borges M et al. 2021). Various other agents are under trial for the management of urticaria and medical history is waiting to witness a path breaking discovery that would finally put an end to this enigmatic ailment.

Last Few Words

Urticaria is one of the most common problems faced by dermatologist in day-to-day practice. Though most of the cases are amenable to treatment, some are resistant to all sorts of known therapeutic manoeuvres. This happens because of our lack of understanding the aetiology of the ailment. Since early days almost all system of medicine confronted with this problem and tried to find out the way to relieve the suffering of the ailing people. With the advancement of modern medical science, one after another puzzles are getting solved. Though the latest modern investigative technology has taken the centre stage in the medical research, but the experience gained through millennia should be exploited instead of setting it aside as mere history, lest we may miss something invaluable which could have been thrown light in the management of this enigmatic disorder.

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