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A history of immune and neuroendocrine system interactions

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Abstract

The purpose of this chapter is to provide a 20th century history of neuroendocrine and immune systems and interactions of their components. The ideas of immune and neuroendocrine structure-function relationships emerged in the life sciences once the cell had become the fundamental unit of life, in large part due to the use of improved microscopes and tissue-staining techniques. In addition, throughout the 20th century, the study of immunity and neuroendocrinology has been guided by the idea of receptor molecules showing specificity for certain biological components. Interestingly, the very notions of neuroendocrine and immune systems, reminiscent of those still used today, were only explicitly formulated in the 1970s. While initial thinking about neuroendocrine-immune interactions in the 1970s-1980s was mostly framed in terms of systems, subsequent physiologic and evolutionary research indicated that these interactions can also occur at the organ, tissue, cellular and molecular levels and that the very labels of immune and neuroendocrine need to be used with caution in present-day and future research.

Keywords: biological systems, history of science, intercellular communication

Glossary

Biological system: Notion referring to a combination of bodily tissues or organs having the same characteristics in physiology.

Cell theory: Theory stipulating that cells are the basic structural, functional, and organizational units of livings organisms, that cells divide to pass on hereditary information and that energy flows within and between cells of an or different organism(s) to maintain life.

History of scientific ideas: A history of science that highlights the role of concepts, hypotheses and theories to account for changes over time in a field of science.

History of scientific techniques: A history of science that focuses on and emphasizes the role of observational and measurement instruments, experimental approaches and technologies employed in a field of science to describe its evolution.

Intercellular communication: Signals exchanged between cells that allow them to regulate and coordinate one another's behavior.

1.1. Introduction: why and what history?

The question of why history of science would be important can receive many answers, ranging from mastering the literature and knowing the origin of a technique to describing the concepts at work in a field. One reason to consider the history of interactions between the immune and neuroendocrine systems from the second half of the 19th century onwards and in particular in the 20th century is that the notions of immune and neuroendocrine have been linked to the idea of the cell being the fundamental unit of life during that period with the help of different kinds of techniques and instruments. An attempt is thus made to give space both to the history of ideas and to that of techniques.

1.1.1. History of techniques prior to WWII

Improvement of microscope and coloration techniques at the end of the 19th century turned out to be revealing for immune and neuroendocrine cells as several of the histological stains made particular cells stand out. As is well known, Ramon y Cajal modified the silver stain developed by Camillo Golgi and applied it to many parts of the central and peripheral nervous systems. Thus, he showed in the last decade of the 19th century that visceral ganglia of rodents, using Meissner plexus as an example, contain cells with short and long cellular ramifications that seem to terminate between smooth muscle cells and close to gland cells in the intestine (Ramon y Cajal, 1893). In these innervated gastrointestinal glands, the granule-rich cell type that stained with eosin, with chromium salts (hence enterochromaffin cells) and with silver nitrate were proposed to be endocrine cells in the early 20th century (Ciaccio, 1906, Masson, 1914, Masson, 1928). Another important line of research that has its origins in observation of stained tissue was the characterization of hypothalamic neurons projecting to the posterior part of the pituitary. Even though these connections had been hypothesized before, Ramon y Cajal showed their existence using Golgi staining in 1894 (Ramon y Cajal, 1911), pp. 488-490).

Another, more physiological, research tradition at the end of the 19th century can be considered to have started with the publication by Oliver and Schaeffer of a short report on the effects of pituitary extracts on blood pressure. They found that pituitary extract just like adrenal extract rapidly increases blood pressure (Oliver and Schafer, 1895). This finding could be reproduced using posterior pituitary extracts and was considered to not be mediated by the sympathetic nervous system or adrenaline (Dale, 1906, Dale, 1909). In parallel, the effects of total removal of the pituitary were being studied in dogs (Paulescu, 1907, Crowe et al., 1909) and partial hypophysectomy was even proposed as an experimental treatment for patients suffering from acromegaly (Cushing, 1909), which in adults is characterized by increased bone size in hands, feet and face. In laboratory rats, hypophysectomy-

induced adrenal, ovarian, testicular and thyroid atrophy as well as dwarfism could be reversed by administration of anterior pituitary extract (Smith, 1930). These findings stimulated other groups to study the effects of different factions of anterior pituitary extracts and led to the isolation of adrenotropic, gonadotropic, growth and thyrotropic hormone-containing fractions (Anderson and Collip, 1933, Collip, 1933, Collip et al., 1933a, Collip et al., 1933b, Anderson and Collip, 1934).

While the influences of the pituitary on other glands in the body became progressively clear using lesion, isolation and replacement techniques, the effects did not seem to be fully specific to the pituitary as some pituitary-sparing ventral hypothalamic lesions also induced genital atrophy (Camus and Roussy, 1920, Bailey and Bremer, 1921, Smith, 1926, Harris, 1937). Geoffrey Harris therefore compared the effects of electrical stimulation of the *tuber cinereum* region of the hypothalamus to those of pituitary stimulation and found that both stimulated ovulation in rabbits (Harris, 1937), p. 392). In discussing these findings, he raised the possibility that "the hypothalamus controls the secretion of hormones … from the anterior lobe [of the pituitary]" (Harris, 1937), p. 392).

Using an improved microscope to observe tissues stained with, amongst other things, aniline dyes, Elie Metchnikoff was able to develop his "comparative pathology of inflammation" and to distinguish different leukocytes at the dawn of the 20th century (Metchnikoff, 1893). Paul Ehrlich had developed many of these stains during his thesis and had also used them to characterize different types of leukocytes (Ehrlich, 1880). In the final decades of the 19th century it was shown that body fluids of animals inoculated with bacteria could lyse bacterial cells, neutralize bacterial toxins or precipitate bacterial products (Nuttall, 1888, Von Behring and Kitasako, 1890, Pfeiffer, 1894). Importantly, the bactericidal activity could also be studied in culture dishes. Such *in vitro* approaches allowed not only to establish that blood serum contains more bactericidal activity than peritoneal exudate (Bordet, 1895, Bordet, 1909), but also to distinguish two active components, a "bactericidal substance," which can be inactivated by heating to 55°C and a "preventive substance," the activity of which resisted heating in different laboratories as shown by Jules Bordet and Paul Ehrlich (Bordet, 1909), pp. 75-80).

At the very end of the 19th century, Paul Ehrlich advanced one of the first formulations of his side chain theory (see below) to provide a hypothetical chemical explanation of the specificity of antibody-antigen reactions. In 1900, Karl Landsteiner decided to systematically study the thus far anecdotal reports of human sera lysing human red blood cells and identified three types, A, B and C (that later became our blood groups with Landsteiner's type C being our group AB) with types A and B lysing red blood cells of other type and type C lysing no other cell types (Landsteiner, 1901, Landsteiner, 1961). Later in his career, Landsteiner undertook a series of studies in which he varied the chemical properties

of antigen and that led him to conclude in 1928 that "the steric configuration of antigenic groups is one of the factors determining serological specificity" (Landsteiner and van der Scheer, 1928), p. 320). When he was awarded the Nobel Prize for Medicine or Physiology for his work on blood groups in 1930, Landsteiner indicated links between his two lines of research as well as the implications of the existence blood groups for transfusions (Landsteiner, 1930). So while the chemical nature of immune reactions would remain elusive for some more decades, progress was made by the systemic study of some variables independently from Ehrlich's influential side chain theory.

1.1.2. History of ideas prior to WWII

The germ theory formulated by Pasteur and like-minded scientists and physicians at the end of the 19th century was subsequently developed to link specific tissue lesions to specific microbes. In this respect, the emergence of the cell theory in the second half of the 19th century can be proposed as a starting point for considering the history of the neuroendocrine and immune systems. In his "remarks on microorganisms" and "their relation to disease", Joseph Lister referred to work of both Robert Koch and Louis Pasteur and echoed Pasteur's question on what part of bacteria were required to confer "immunity from further attacks of … disease" (Lister, 1880), p. 364). At the turn of the 19th century, Lister discussed how application of his "antiseptic system" allowed to eradicate "hospital gangrene" and gave credit to "Pasteur [who] saw the analogy between the immunity to fowl-cholera produced by its attenuated virus and the protection afforded against small-pox by vaccination" (Lister, 1896), p. 418, p. 421). Finally, he addressed "a subject which, though not bacteriological, has intimate relations with bacteria" and related observations by Elie Metchnikoff indicating "that the microbes of infective diseases are subject to [a] process of devouring and digestion, carried on both by the white corpuscles and by cells that line the blood vessels" as a means of defense (Lister, 1896), pp. 427-428).

In the early 20th century, Ernest Starling introduced the term 'hormone' to refer to chemical messengers that "have to be carried from the organ where they are produced to the organ which they affect by means of the blood stream" to meet "the continually recurring physiological needs of the organism" (Starling, 1905), p. 340). He continued to promote the concept after the first World War and proposed in a lecture entitled *The wisdom of the body* that, in addition to the growth-promoting secretion of the anterior pituitary, "[t]he posterior lobe … forms one or more substances which, circulating in the blood, have the most diverse influences on various parts of the body" (Starling, 1923), p. 689). Thus, he raised the idea that the posterior pituitary could not only communicate via cellular connections with the hypothalamus, but also via humoral means by releasing mediators into the blood stream. A decade later, Harvey Cushing considered that there "appear to be two routes, both probably

under nervous control, whereby the products of pituitary secretion are transported to the tuberal and possibly to other nuclei of the anterior hypothalamus: (i) from pars anterior by way of the "hypophysio-portal" vessels; and (2) from pars intermedia by way of the tissue" (Cushing, 1933), pp. 540-541).

These consideration can be taken to be part of a more general debate in the first half of the 20th century regarding the modalities of intercellular communication, in particular between nervous and endocrine signal transmission. For example, histochemical stains seemed to indicate the presence of gland-like nerve cells in several invertebrate ganglia and parts of the vertebrate central nervous system (Scharrer, 1928, Scharrer and Scharrer, 1937). Interestingly, similarities between the effects of administration of adrenal extracts and electrical stimulation of the sympathetic nervous system had repeatedly been pointed out, for example by John Langley and Walter Cannon (Langley, 1901, Cannon, 1914, Cannon, 1927), pp. 36-38). In addition, it was reported that systemic administration of brain and intestinal tissue extracts in rabbits lowered blood pressure in ways that could not be explained by the action of actetylcholine or adenosine (Von Euler and Gaddum, 1931). These findings not only indicated the discovery of a new substance, coined P, but also the possibility that the same intercellular messengers exist in the brain and the intestine. In this respect, another important, but often overlooked aspect, is the possibility that gastrointestinal tract epithelia constitute a diffuse endocrine organ in close interaction with nerves as put forward by Friendrich Feyrter in 1938 (Feyrter, 1938). Feyrter compared ductal cells of the pancreas and enterochromaffin cells of the gastrointestinal tract and observed that both responded similarly to different kind of stains (among which Masson's silver stain). Based on these observations, he proposed that endocrine-like signals could not only be produced by specialized glands, such as the pancreas and pituitary, but also by surface epithelia. In addition, Feyrter suggested, based on Cajal's and Masson's findings mentioned above, that the cells of the diffuse endocrine organ of the gastrointestinal tract were connected to local neural fibers.

1.2. Post World War II success stories of immunology and neuroendocrinology

1.2.1. Connecting the hypothalamus and pituitary

Right after World War II (WWII) it seemed established that the release of the so-called antidiuretic hormone from the posterior pituitary in response to emotional stress was linked to "stimulation … of the supraoptic, and possibly of the paraventricular nuclei [of the hypothalamus], whose axons pass down the stalk to the pars nervosa [of the pituitary]" (Verney, 1947), p., 99). This hypothesis of hypothalamic neuron-derived hormonal messengers being released in extracerebral organs was subsequently corroborated by findings confirming the anatomical continuity between cell bodies of

hypothalamic nuclei and the posterior pituitary based on a new histological stain and the effects of interruptions of the pituitary stalk connecting the two (Bargmann and Scharrer, 1951, Hild, 1951).

Geoffrey Harris in the 1930s had postulated, based on stimulation experiments, that "the hypothalamus controls the secretion of hormones … from the anterior lobe [of the pituitary]" (Harris, 1937), p. 392). A decade later, in a review article, he first argued regarding direct nerve supply and control of endocrine glands that the posterior pituitary and adrenal medulla are exceptions in that they may developmentally be considered as extensions of the central and peripheral nervous systems (Harris, 1948). Harris next summarized evidence of lesion and stimulation studies indicating neural control of the anterior pituitary or adenohypophysis, but pointed out that "[t]he mechanism whereby this neural control is exerted is uncertain" (Harris, 1948), p. 157). Furthermore, Harris related reports, including his own work, indicating "a true portal system of blood vessels in the pituitary stalk" with blood flowing from the median eminence of the hypothalamus to the anterior pituitary (Green and Harris, 1949), p. 360) to raise the possibility that "nervous stimuli might cause the liberation of some substance into the capillary sinusoids of the median eminence" and that "this substance [is] transported via the hypophysial portal vessels to excite or inhibit" pituitary secretions (Harris, 1948), p. 168, p. 169). Finally, he proposed that the neuronal and hormonal links of the hypothalamus with respectively the posterior or neurohypophysis and the anterior pituitary or adenohypophysis mediate different functions (Harris, 1951a, Harris, 1951b). Thus, Harris' work laid the foundation for envisioning some new structure-function relationships in biology.

1.2.2. Study of immunity between chemistry and biology

Immunology had taken a chemical turn before WWII with debates about the nature of the chemical bond or affinity that occurred between bacterial toxins and antibodies. The idea that chemistry was essential to the advancement of immunology was widespread after WWII. For example, one could read in a medical journal that: "The phenomena of immunity are essentially chemical, and we might reasonably expect that some of its problems will soon be solved if a more sustained chemical and biochemical attack is made on them" (Wormall, 1948), p. 333). Chemical approaches were not only expected to further the understanding of antigen-antibody binding, but also that of phagocytosis, blood groups and complement reactions (Wormall, 1948). Indeed, one important way in which chemistry allowed immunology to make progress was through the development of new quantitative methods for the study of antigen-antibody, blood group and complement reactions (Mayer, 1951). Another physicochemical technique that proved useful to further characterize various protein immune components was John Cohn's chemical fractionation of blood plasma (Cohn et al., 1944). However,

chemistry in the immediate post-WWIII years did not really provide many answers to immunological problems encountered in the clinic, such as autoimmunity as well as host rejection of blood transfusion and organ and tissue transplantations.

During the 1940s, the Australian virologist Frank Macfarlane Burnet started to make important conceptual contributions to the field of immunology. In his *Biological aspects of infectious disease*, Burnet stated that "a conflict between man and his parasites… in constant environment, would tend to result in a virtual equilibrium," but that because "[m]an lives in an environment constantly being changed by his own activities … few of his diseases have attained such an equilibrium" (Burnet, 1940), p. 23). Another interesting aspect of Burnet's thinking emerged after observing amoebal digestion (like Metchnikoff more than half a century earlier). Thus, Burnet remarked that: "The fact that the one is digested, the other not, demands that in some way or other the living substance of the amoeba can distinguish between the chemical structure characteristic of "self" and any sufficiently different chemical structure which is recognized as "not-self" (Burnet, 1940), p. 29). He developed this idea more in *The production of antibodies* and pointed out that: "It is an obvious physiological necessity and a fact fully established by experiment that the body's own cells should not provoke antibody formation" (Burnet and Fenner, 1949), p. 85). Finally, he noted that "[i]mmunology has through most of its history been remote from the general stream of biological discovery and generalization" and urged that "immunological phenomena and interpretations must be given due weight in any future formulations of the nature of living process" (Burnet and Fenner, 1949), pp. 132-133). Thus, Burnet, in the course of the 1940s, elaborated a vision on immunology that was complementary to the chemical discourse of the time.

1.2.3. Characterization of some hypothalamic releasing factors and pituitary hormones

An influential vision of neuroendocrinology was articulated by Geoffrey Harris in his 1955 *Neural control of the pituitary gland* monograph in which he suggested that neuroendocrine neurons were motor or effector neurons. He also proposed functional criteria for determining if an endogenous substance constitutes a releasing factor at the level of the anterior pituitary (Harris, 1955). Interestingly, the same year, Roger Guillemin and Barry Rosenberg proposed "[t]he possibility of investigating this problem by simple *in vitro* techniques" consisting of culturing fragments of the pituitary gland along with those of the ventral hypothalamus (Guillemin and Rosenberg, 1955), p. 599). In parallel, it was established that adrenocorticotropin hormone (ACTH), the active principle secreted by the anterior pituitary controlling adrenal cortical structure, weight and secretion, corresponds to a 20 kDalton protein (Morris, 1951). Around the same time, it was also shown that some steroids

secreted by adrenal cortex, like 17-hydroxy-1 1-dehydro-corticosterone soon to become better known as cortisone or cortisol, have the same beneficial effects as ACTH on arthritis (Hench et al., 1949). Moreover, Vincent du Vigneaud and colleagues found in 1954 that a nine cyclic amino acid peptide they synthesized had the same physicochemical and biological properties as the 'oxytocic substance of the neurohypophysis' (see above) and therefore concluded to "the identity of the synthetic product with natural oxytocin" (du Vigneaud et al., 1954), p. 3115). The same group established that oxytocin differs by only two amino acids form vasopressin and that the posterior pituitary hormone that increases blood pressure also promotes water retention (see above; (Katsoyannis and Du Vigneaud, 1958). Interestingly, Murray Saffran and Andrew Schally also identified a peptide in hypothalamic and posterior pituitary extracts, coined Corticotropin-Releasing Factor (CRF) that is different from vasopressin but induces ACTH secretion from rat anterior-pituitary tissue *in vitro* (Saffran and Schally, 1955b, Saffran and Schally, 1955a, Schally et al., 1958). Furthermore, arterial perfusion of isolated adrenal glands also enabled to establish that vasopressin, but not oxytocin, has the same effects as ACTH on hydrocortisone secretion (Hilton et al., 1960). Thus, while the 1950s witnessed a consolidation of findings obtained by classical experimental approaches that allowed to formulate a first conceptual neuroendocrinological framework, it also saw the development of new *in vitro* and biochemical methods relevant for the future development of neuroendocrinology.

1.2.4. Tolerance and antibody production

Besides his theoretical contributions, Burnet was also well-versed in biochemical, genetic and microscopic approaches and often combined these to address scientific questions. For example, chick embryos allowed him to study clumping or agglutination of blood cells when mixed with fluid of influenza-infected individuals and to use this phenomenon to generate hypotheses "on the process of interaction between the virus and the cell" (Burnet, 1952), p. 229). Chick embryo preparations had long been used and were known to allow for grafting and growing of mammalian cells and tumors (Murphy, 1913), a phenomenon that Burnet coined tolerance (Burnet, 1941), p. 45). Interestingly, Burnet subsequently showed that chick embryos are also unable to produce antibodies after inoculation of influenza virus (Burnet et al., 1950).

Burnet's immature immune tolerance concept was progressively supplemented with Peter Medawar's ideas on this matter. Medawar was one of the physicians who had explored the possibility of skin transplantation to treat burns during WWII (Gibson and Medawar, 1943). In a 1948 article discussing the contribution of tissue culture methods to elucidate "the nature of immunity against transplanted skin," he clearly stated the problem by remarking that: "When skin is grafted from one human being

or one rabbit to another, a 'defence' mechanism is called into action which leads, in due course, to the complete destruction of the foreign grafted tissue" (Medawar, 1948), p. 239). Medawar next indicated that this reaction "varies with the antigenic relationship between donor and recipient" and that "[skin transplantation immunology] conformed … with the pattern of immunity created by bacterial and other crudely foreign antigens" (Medawar, 1948), p. 239). A couple of years later, with colleagues, he claimed to have found "a 'laboratory' solution-of the problem of how to make tissue homografts immunologically acceptable to hosts, which would normally react against them" (Billingham et al., 1953), p. 603). Medawar and colleagues interpreted their findings based on experiments with mouse foeti and chick embryos to show "that mammals and birds never develop, or develop to only a limited degree, the power to react immunologically against foreign homologous tissue cells to which they have been exposed sufficiently early in foetal life" (Billingham et al., 1953), p. 603). The work by Burnet and Medawar was rewarded the 1960 Nobel prize for medicine or physiology for "for [the] discovery of acquired immunological tolerance" (Committee, 1960).

While the multiple binding sites of antibodies (Marrack et al., 1951) and "the structure of antigen-antibody aggregates and complement fixation" (Marrack, 1955), p. 369) were progressively being understood in the 1950s, this was less the case for the mechanism of antibody production (Stallybrass, 1950). In 1941, Burnet had postulated 1) that "production of antibody is quite certainly not a multiplication of antibody molecules in the blood plasma, but a cellular phenomenon," 2) that "each antigen molecule makes contact with a cell "sensitized" by previous contact with antigen [and] sets going a change in the cell so that after a suitable latent period the cell liberates a series of antibody molecules," and 3) that the logarithmic character of this response "is because the entities concerned are either themselves multiplying or are being produced by multiplying agent" (Burnet, 1941), p. 23). Niels Jerne next proposed his natural selection theory of antibody formation, according to which antigen is "a selective carrier of spontaneously circulating antibody to a system of cells which can reproduce this antibody" so that "[a]ntigen, secondarily introduced into the circulation, now meets a larger concentration of specific molecules and carries a larger quantity of these, selected for the better-fitting ones, to the antibody-producing apparatus" (Jerne, 1955), pp. 849-850). Accordingly, he put forward that: "In the absence of antigen no directional pressure is imposed upon globulin synthesis, and it seems reasonable to assume that a great variety of configurations, due, perhaps, to various amino acid sequences at the specific sites of the globulin molecules, may develop at random" (Jerne, 1955), p. 851). Burnet postulated, in turn, that "when antigen-natural antibody contact takes place on the surface of a lymphocyte the cell is activated to settle in an appropriate tissue, spleen, lymph node or local inflammatory accumulation, and there undergo proliferation to produce a variety of

descendants" and referred to this idea as the "clonal selection hypothesis" (Burnet, 1957), pp. 68-69).

In the early 1960s, important structural elements with respect to antibody function were unraveled by Gerald Edelman and colleagues combing ultracentrifugation fractioning under different reducing conditions, chromatography and electrophoresis separation and ion exchange chromatography-based amino acid analysis(Edelman and Poulik, 1961). These authors concluded 1) that the different subunits of antibodies were held together by disulfide bonds, 2) that "antibodies of different specificity consist of different types of polypeptide chains," (Edelman et al., 1961), p. 1757and 3) that "[t]he antigenic cross-reactivity among the classes would be accounted for by the general structural similarity of their [light] chains" of around 20,000 (Edelman and Benacerraf, 1962), p. 1039). While broadly subscribing to Burnet's views on antibody formation, some authors speculated that "[t]he genic diversity of the precursors of antibody-forming cells arises from a high rate of spontaneous mutation during their lifelong proliferation" (Lederberg, 1959), p. 1650). More elaborated hypotheses accounting for the degree of antibody diversity invoking the combined effects of gene duplication, point mutations and somatic recombination were thus formulated at the end of the 1960s (Edelman and Gally, 1967, Smithies, 1967).

1.2.5. Neuroendocrinology as a discipline

The development of electron microscopy and ultra-centrifugation allowed both scientists with a background in anatomy as well as those with a training in biochemistry to advance their studies in the 1960s. Using electron microscopy, sometimes combined with ultracentrifugation, different groups obtained evidence indicating that nerve endings are indeed present in the posterior pituitary (LaBella and Sanwal, 1965, Rodriguez and Dellmann, 1970). Observations of preparations under the electron microscope also enabled various independent confirmations of the existence of neurosecretory vessels in the median eminence in proximity to the portal vessels running to the anterior pituitary (Rinne, 1960, Mazzuca, 1964, Wittkowski, 1967).

Interestingly, using an array of biochemical approaches including centrifugation, a protein isolated from the hypophyseal portal vessel system was also found to stimulate adrenocorticoptropin hormone release and could therefore be considered a CRF (Porter and Rumsfeld, 1959). A physiological 'tour de force' was realized by Averill and colleagues, who showed that hypophyseal portal vessel blood of rats, in response to electrical stimulation of the hypothalamus, contained a Thyrotrophin Releasing Factor (TRF) that promoted Thyroid Stimulating Hormone production after administration into the rabbit pituitary circulation (Averill et al., 1966). In parallel, several groups were engaged in a 'biochemical

race' to extract, purify and identify this TRF, with Andrew Schally's group proposing, based on extracts of 100,000 porcine hypothalami, a substance that was for 30% composed of amino acids (Schally et al., 1966), while Roger Guillemin's group claimed to have obtained, from 270,000 sheep hypothalami, a compound that was for 80% composed of three amino acids (Guillemin et al., 1965). But beyond, or perhaps, in part, because of, this scientific dispute, neuroendocrinology started to enjoy some recognition with review articles in major scientific and medical journal and books being published under that banner (Reichlin, 1963a, Reichlin, 1963c, Reichlin, 1963b, Scharrer and Scharrer, 1963). Furthermore, the journal Neuroendocrinology was launched in the mid-1960s as an outlet for articles "with the unifying concepts and the common denominators of neuroendocrinology" after "[n]euroendocrinology has gained recognition as a field of research in its own right" (Scharrer, 1965).

As noticed above, the starting points of many of the anatomical and biochemical approaches were the effects of lesion of glands or injection of gland extracts on water and mineral physiology, growth, sexual maturity and lactation. Progressively, after WWII, these effects were thought to be mediated by functional axes formed by the hypothalamus, the pituitary (anterior and posterior) and endocrine glands, for example of the adrenal and thyroid. Indeed, one can encounter the first mention of a hypothalamo-pituitary-adrenal (HPA) axis on PubMed in the late 1960s, that of the hypothalamo-pituitary-gonadal (HPG) axis in the early 1970s, and that of a hypothalamo-pituitary-thyroid axis in the mid-1970s. In addition, a new physiological and behavioral concept progressively linked to the HPA axis was put forward by Hans Selye from the 1950s onwards in the form of the stress response (Selye, 1950, Selye, 1976). In parallel to these hypothalamus-controlled neuroendocrine axes, it was shown, using anatomical and cytochemical approaches, that enteroendocrine cells share characteristics with pituitary corticotroph cells and pancreatic islet cells, known to secrete polypeptide hormones (Pearse, 1968, Pearse, 1969, Pearse and Polak, 1971). These observations indicate that enteroendrocine and pituitary cells may share secretory mechanism of polypeptide hormones and thus raises the question of the physiological functions of such mechanisms in the gastro-intestinal tract.

1.2.6. Antibodies as tools

In the early 1950s, the improved method developed by Albert Coons and Melvin Kaplan for conjugation of the fluorescent marker fluorescein to antibody made it possible for this group to localize antigens and antibodies in tissues (Coons and Kaplan, 1950, Coons et al., 1950, Coons et al., 1951, Coons et al., 1955). Over the following decade, this technique became very popular (Coons, 1961). Antibody conjugation approaches were subsequently expanded to enzymes, which enabled to obtain more permanently stained tissues and to circumvent the problems of fluorophore fading and

autofluorescent tissues (Nakane and Pierce, 1967). In the 1970s, the use of different fluorescent labels conjugate to different antibodies also allowed to sort and concentrate cell populations (Bonner et al., 1972, Julius et al., 1972). All of the approaches were further improved after monoclonal antibodies with predefined specificity became available (Koehler and Milstein, 1975). The fluorescence activated cell sorter (FACS) was to become an essential tool in immunology and even gave rise to the CD international classification of white blood cells.

Not surprisingly, given the peptidergic nature of many hormones, many attempts were undertaken to develop antibody-based detection techniques of these mediators in bodily fluids and tissue extracts (Yalow and Berson, 1960, Utiger et al., 1962, Felber, 1963, Spitzer, 1968). Thus, so-called radioimmunoassay were employed to study the effects of potential hypothalamic releasing factors on pituitary contents of growth hormone or ACTH (Rodger et al., 1969, Brazeau et al., 1973, Rivier et al., 1973). Alternatively, these assays were also used to detect luteinizing hormone-releasing hormone and TRH in the hypothalamus and the cerebrospinal fluid (Ishikawa, 1973, Brownstein et al., 1974, Palkovits et al., 1974). Furthermore, immunohistochemical techniques employing antisera raised against polypeptide hormones allowed to show the presence of such immunoreactive material not only in enteroendocrine cells, but also in the brain, beyond the hypothalamus (Barry et al., 1973, Leonardelli et al., 1973, Polak et al., 1974a, Polak et al., 1974b, Gross, 1976, Gross and Baker, 1977, Fuxe et al., 1977). Thus, these new antibody-based techniques made it possible to refine both biochemical and anatomical approaches in neuroendocrinology.

1.2.7. The recognition of neuroendocrine systems

The 1970s were a decade during which neuroendocrinology was the object of important conceptual developments and also received important marks of scientific respectability. Indeed, the book series Progress in Brain Research dedicated two volumes to neuroendocrinology between 1970 and 1973, the first on the *Pituitary, adrenal and the brain* and the second on *Drug effects on neuroendocrine regulation*. In the latter volume, John Porter looked at the history of neuroendocrinology and asked "what precisely is a neuroendocrine system?" (Porter, 1973), p. 1) He proposed that "[a] neuroendocrine system consists of a neural cell or cells which secrete into the extracellular fluid a substance which upon reaching other cells modify their behavior" (Porter, 1973), pp. 2-3). Porter also specified that his "definition does not exclude the possibility that non-neuronal cells may also be neurosecretory cells" and that "it does not require that the secretory product be transported through blood" (Porter, 1973), p. 3) to raise the possibility that cerebrospinal fluid could constitute a medium for neuroendocrine signals.

Another sign of scientific recognition was the tribune in the journal Nature offered to Anthony Pearse, who had previously pointed out anatomical and cytochemical similarities between enteroendocrine cells, pancreatic islet cells and pituitary corticotroph cells. In his review, Pearse first reminded the reader of the discovery of the existence of a same substance, coined P, in the brain and intestine by Von Euler and colleagues in the 1930s before relating his own recent work as well as that by others showing that the same is true for other peptides, like somatostatin and vasoactive-intestinal peptide, and reiterating the question of a possible common embryologic origin (Pearse, 1976). In a subsequent chapter title, he then proposed the term “diffuse neuroendocrine system” and speculated about the different modes of action that the same peptides could have in different biological contexts (Pearse, 1978), p. 49).

The ultimate recognition of the scientific community for neuroendocrinology came in 1977 with the Nobel Prize for physiology or medicine, shared between Roger Guillemin and Andrew Schally "for their discoveries concerning the peptide hormone production of the brain" and Rosalyn Yalow "for the development of radioimmunoassays of peptide hormones" (Commitee, 1978). In his Nobel lecture entitled Peptides in the brain: the new endocrinology of the neuron, Guillemin also mentioned the presence of somatostatin and other peptides in the brain and intestine and joined Pearse in wondering about their possible paracrine and endocrine modes of action (Guillemin, 1978). Finally, at the turn of the decade, Pearse’s colleagues Julia Pollak and Steve Bloom elaborated on the idea of “the neuroendocrine design of the gut,” proposed a couple of years earlier (Makhlouf, 1974, Polak and Bloom, 1979b), and referred to the “diffuse neuroendocrine system” as a “powerful controlling system” (Polak and Bloom, 1979a), p. 1400). So, important theoretical progress was made by proposing a definition of neuroendocrine systems that grouped both the hypothalamo-pituitary-end organ axes as well as gastrointestinal enteroendocrine cells.

1.2.8. A formulation of the immune system

In 1968 an important distinction of lymphocyte populations was proposed between bone marrow-derived cells (or B-cells), which become antibody producing cells, and thymus-derived cells (later shortened to T-cells), which only help in antibody production (Miller and Mitchell, 1968, Mitchell and Miller, 1968a, Mitchell and Miller, 1968b). Interestingly, in the early 1970s, Niels Jerne updated his natural selection theory of antibody formation by postulating that the selection process “of mutant cells expressing []genes that have been modified by spontaneous random somatic mutation” occurs in the thymus (Jerne, 1971), p. 1). Subsequently, he published a series of theoretical articles in which he

proposed a conceptual view of the immune system. While the very term “immune system” had been used before, including in publication on the ontogeny of the thymus, it was often not elaborated beyond its mention (Metcalf and Brumby, 1966, Tyan, 1968, Tyan and Herzenberg, 1968). Jerne, instead, argued that “[t]he immune system is comparable in the complexity of its functions to the nervous system” in that both “respond adequately to an enormous variety of signals,” and “[b]oth systems … learn from experience and build up a memory” (Jerne, 1973). In a follow-up paper, Jerne concluded that “the immune system, even in the absence of antigens … achieves a dynamic steady state as its elements interact between themselves” (Jerne, 1974), p. 383). These "theories concerning the specificity in development and control of the immune system” were the main motivation to award Jerne the Nobel Prize in 1984 (Committee, 1984). So, like for the neuroendocrine system, important theoretical progress led to the explicit proposal of what the immune system is and does.

1.3. A history of neuroendocrine-immune interactions

Historically speaking it is interesting to note that most of the work on interactions between the neuroendocrine and immune occurred once these adjectives referred to systems, even though (neuro)endocrine and immune cells had long been known. This may seem even more surprising given that some of the leading immunologists, like Niels Jerne, had remarked concerning the immune and nervous systems that “[t]he two systems penetrate most other tissues of our body, but they seem to be kept separate from each other by the so-called blood-brain barrier.” (Jerne, 1974), p. 387) and that “a population of lymphocytes … in appropriate tissue culture fluid” stimulated with antigen “will produce specific antibody molecules, in the absence of any nerve cells (Mishell and Dutton, 1967)” (Jerne, 1985), p. 852). However, it can also been argued that it was necessary to have some clearer understanding of systems’ structure and function before interactions could be envisioned.

1.3.1. Conditioning immune responses

Conditioning of a behavioral or physiological response to neutral stimuli, (which are “conditions [that] do not trigger a response [initially]”) is considered to be related to the presence of a central nervous system (Ginsburg and Jablonka, 2021), p. 5). Interestingly, classical conditioning of leukocyte and antibody responses had already been shown in the early 20th century (Metalnikov and Chrorine, 1926, Metalnikov and Chrorine, 1928). However, probably because many of the follow-up studies were done in the Soviet Union and Eastern Europe, the findings of such experiments were only noticed in the Western world after the 1970s when Robert Ader and Nicolas Cohen showed that the immunosuppressive effects of certain drugs could be conditioned (Ader and Cohen, 1975, Ader and Cohen, 1982, Pacheco-López et al., 2007). Not surprisingly, a review article published in 1985 stated

that “[t]he traditional view that the nervous and immune systems are functionally independent … is being challenged” by the “possib[ility] to change the activity of the immune system by means of Pavlovian conditioning, just as it is possible to condition other physiological events influenced by the autonomic nervous system or neuroendocrine substances” (Brittain and Wiener, 1985), p. 181).

1.3.2. Stressing corticotropic influences on immune responses

While the anti-inflammatory effects of glucocorticoids had been known since the 1950s (Gordon and Katsh, 1949, Glyn, 1998), there were also some indications, that could be interpreted to suggest that ACTH may influence immune cell counts and antibody production (Harris, 1951b, Mayer, 1951, Morris, 1951). Interestingly, in the early 1970s, it was shown that prior hypophysectomy leads to a subsequent depression of spleen immune responses to antigen *in vitro* (Gisler and Schenkel-Hulliger, 1971). However, these effects have not been easy to reproduce *in vivo* (Kalden et al., 1970). Similarly, the reported consequences of lesions of the hypothalamus on antibody responses and their dependence on the pituitary and corticosteroids have been highly variable (Stein et al., 1976, Cross et al., 1980, Cross et al., 1982). Nevertheless, a vision started to emerge according to which the neuroendocrine and immune systems interact after it was shown that the administration of two classic antigens in rodents, namely sheep red blood cells and hemocyanin, results in increased electrophysiological activity in the hypothalamus (Besedovsky et al., 1977). It has been argued that such a vision “bring[s] the self-regulated immune system into conformity with other body systems” and “is based on the existence of afferent-efferent pathways between immune and neuroendocrine structures” (Besedovsky and Sorkin, 1977), p. 1). Thus, in the same year that Jerne announced that “a population of lymphocytes … in appropriate tissue culture fluid” stimulated with antigen “will produce specific antibody molecules, in the absence of any nerve cells” (Jerne, 1985), p. 852), others affirmed that “hormones, neurotransmitters, and neuropeptides [released] in the microenvironment of immunologic cells” can provide “external immunoregulatory signals imposed upon autoregulatory mechanisms” (Besedovsky et al., 1985), p. 750s).

This emerging framework of neuroendocrine-immune interactions also provided a potential biological substrate for the reported effects of stress on disease. Furthermore, it had become clear, between the 1950s and 1970s, that acute and chronic stress were associated with increased corticosteroid production in animals, including humans (Hale et al., 1957, Mason et al., 1961, Treiman et al., 1970, Weiss, 1970, Arguelles et al., 1972, Bassett et al., 1973, Tache et al., 1976). Not surprisingly, in the second half of the 1970s several authors therefore concluded that “psychosocial processes influence the susceptibility to some infections, to some neoplastic processes, and to some aspects of humoral

and cell-mediated immune responses" (Stein et al., 1976), p. 439) and that "[t]hese psycho-social effects may be related to hypothalamic activity, the autonomic nervous system, and neuro-endocrine activity" (Miller, 1977), p. 413). However, given that "[t]he term "stress" has been used in so many different ways", it is important to specify, for example, that the "focus [is] on psychological stress rather than physical stresses such as starvation or exposure to extreme cold" (Rogers et al., 1979), p. 147, p. 153). Thus, it could be concluded at the end of the decade that "[t]here seems little doubt that different psychological states … can influence the immune system" and that "[t]he questions now are really what the mechanisms are, and how clinically significant they might be" (Rogers et al., 1979), p. 158). Regarding the latter, "[t]he predominant hypothesis has been that CNS change leads to immunologic change through the mechanism of hypothalamic-pituitary hormonal stimulation" (Rogers et al., 1979), p. 158). Interestingly, the idea that psychological stress alters the immune system through activation of the neuroendocrine system has been a working hypothesis for many years (Stein et al., 1985, Tecoma and Huey, 1985).

1.3.3. Shared markers and multilevel neuroendocrine-immune interactions

In addition to immune-neuroendocrine interactions formulated at the systems levels, the findings obtained by different experimental approaches also seemed to indicate other kinds of relationships as well. For example, in spite of the fact that the thymus since the early 1970s had been considered an immune organ, it was found a couple of years later that congenitally athymic (nude) mice and neonatally thymectomized mice show endocrine change indicating that "the thymus may well have a basic role in the organization of the adult hypothalamus-pituitary axis for thyroid and sexual functions" (Pierpaoli and Besedovsky, 1975), p. 323). Moreover, chromogranin, a marker that had been used to propose the notion of the diffuse neuroendocrine system, was also found to be detected in tissues of the spleen, lymph nodes and thymus, thought to be part of the immune system (Angeletti and Hickey, 1985). Other indications that labels like immune, neuroendocrine or neuronal may not neatly characterize our epistemic categories once and for all can also be found in the literature. Thus, it turned out in the early 1980s that immune cells were not only sensitive to mediators like ACTH, which by then was considered a(n) (neuro)endocrine messenger molecule, but could also synthesize them during infection (Johnson et al., 1982, Johnson et al., 1984, Blalock and Smith, 1985). This illustrates that the initial context in which a molecule was discovered (neuroendocrine or immune) is often not the only biological conditions in which it plays a role. Conversely, it was shown that interleukin-1, which was, as its name indicates, thought of as a messenger molecule between leukocytes, can stimulate both pituitary mRNA expression and secretion of ACTH as well as hypothalamic production of corticotropin-releasing hormone (Berkenbosch et al., 1987, Bernton et al., 1987, Brown et al., 1987, Sapolsky et al.,

1987). This illustrates not only that neuroendocrine-immune interactions can happen between molecular and cellular elements of these systems, but also that that these neuroendocrine-immune interactions may occur in parallel with endocrine-immune or lower-level interactions, and thus raises the question of the circumstances under which neuroendocrine-immune interactions occur.

Another example of neuroendocrine-immune interactions concerned the central nervous system action of some interleukins or lymphokines, as they were called in the 1970s and early 1980s before being grouped under the wider-ranging name of cytokines. The first step, in hindsight, was the recognition that brain cells, and in particular glial cells, are capable of producing interleukin-1 *in vitro* and *in vivo* in response to administration of bacterial lipopolysaccharide or local injury (Fontana et al., 1982, Coceani et al., 1988, Hetier et al., 1988). These findings not only led to a revision of the immune-privileged status of the brain, but also to the possibility that interleukin-1 action in or on the brain could play roles other than in response to local injury or infection. Indeed, peripheral administration of purified interleukin-1, obtained after exposure of a macrophage cell line to bacterial lipopolysaccharide, not only stimulates thymocyte proliferation, but also induces fever (Duff and Durum, 1983). The possibility that central interleukin-1 action could play a role in fever induction or neuroendocrine activation has been repeatedly addressed (Fontana et al., 1984, Hooghe-Peters et al., 1991). But, one of the earliest bacterial fragment induced, CNS-regulated host responses, which was shown to both be mimicked and mediated by central interleukin-1 was increased sleep (Krueger et al., 1984, Shoham et al., 1987, Imeri et al., 1993, Takahashi et al., 1996).

And while some of the somnogenic effects of central interleukin-1 are mediated and modulated by hypothalamic releasing factors (Krueger, 1990, Krueger and Obál F, 1993), and can therefore be qualified as neuroendocrine-immune interactions, it turned out that interleukin-1's presumed mode of action may also be considered as neuroendocrine. First, brain interleukin-1 expression and its cerebrospinal fluid concentrations increase during sleep in comparison to the awake state of animals, even in the absence of exposure to microbial fragments (Lue et al., 1988, Taishi et al., 1998). Moreover, central inhibition of interleukin-1 action has been shown to reduce sleep and its rebound after sleep deprivation (Opp and Krueger, 1994, Takahashi et al., 1996, Takahashi et al., 1997). Finally, infusion of interleukin-1 into different parts of the ventricular and subarchnoid cerebrospinal fluid systems allowed for the determination that its maximal sleep-stimulating effects occur at the site where prostaglandin D2, an already known somnogenic substance of which the production can be induced interleukin-1, promotes sleep (Terao et al., 1998). Altogether, it thus seems that interleukin-1, a mediator classically associated with the immune system, plays a role in the physiological regulation of

sleep in the brain, through an endocrine-like mode of action that does not involve the systemic blood circulation, but rather the cerebral ventricular cerebrospinal fluid.

Finally, evolution-inspired considerations can be interpreted to urge some reframing of the way neuroendocrine-immune interactions are understood. Based on immunoreactivity and immunoneutralization studies indicating that "hormonal peptides and neuropeptides … are native to unicellular organisms," "a common phylogenetic origin for the endocrine system and nervous system of vertebrates" was proposed in the early 1980s (Le Roith et al., 1982). The subsequent detection of mediators, which were thought to be hormones and neuropeptides, such as ACTH and beta-endorphin, in immune(-like) cells of mammals, amphibians and gastropods exposed to bacterial fragments gave rise to several hypotheses (Blalock et al., 1985, Ottaviani et al., 1991, Ottaviani et al., 1992). These varied from the suggestions that "the immune and neuroendocrine systems represent a totally integrated circuit by virtue of sharing a common set of hormones" (Blalock et al., 1985), p. 858s) to the proposals that the "immune and neuroendocrine systems share a common evolutionary origin" (Ottaviani et al., 1991), p. 215). The idea of a shared common origin between the neuroendocrine and immune systems could also explain why certain markers thought to indicate neuroendocrine function can be found in immune cells (Day and Salzet, 2002). Thus, it has been proposed that it is necessary "to redefine previous "neuroendocrine" concepts to include the notion that activation of specific genetic switches can lead to the expression of a partial or full neuroendocrine phenotype in a variety of cell types, including immune cells" (Day and Salzet, 2002), p. 447). So while, initial thinking about neuroendocrine-immune interactions seemed to be formulated in terms of systems in the 1970s-1980s, subsequent physiologic and evolutionary research on some of the mediators involved led to the conclusion that these interactions can occur at the organ, tissue, cellular and molecular levels as well and that the very labels of immune and neuroendocrine may need to be revised. A recent illustration of this is the finding that in *Hydra*, an organism that lacks immune cells, neuroendocrine-like cells secrete peptides that control bacterial growth on its epithelial surface (Augustin et al., 2017).

1.4. Perspectives for future research

One of the reasons for looking back at the history of science is the belief that one might learn from it. Regarding history of science itself, the hope is that this chapter has shown that the evolution of scientific fields are neither driven exclusively by technological progress nor solely by conceptual developments. Instead, the histories of immunology and neuroendocrinology and that of the study of neuroendocrine-immune interactions presented here illustrate that both technological progress and conceptual development have played important, but variable, roles throughout the 20th century. For

example, on the one hand, the techniques and technologies for generating antibodies have been instrumental to gain a better understanding of the tissue distribution and changes in body fluid concentrations of molecules of interest in all of these fields. But, on the other hand, the very emergence of the notions of immune and neuroendocrine systems could only occur after certain theoretical considerations regarding systems, regulation and function had taken place. Furthermore, much of the initial excitement and interest regarding neuroendocrine-immune interactions seemed to be fed by the challenges it seemed to pose to then held structure-function relationships of and regulation by immune and neuroendocrine systems.

One of the important general lessons that science can learn from its history is that that the categories, concepts and labels that a field of science proposes to make sense of a part of the world at one point should not be taken to be definitive. One example of this is the expansion of the label 'neuroendocrine' from functional axes involving the hypothalamus, the pituitary and some peripheral glands to more localized organizations in the gastrointestinal system. The gut itself is also a good example of how the functions associated with it have evolved over time. Indeed, throughout most of the 20th century the gut's function was perceived as being mainly digestive and its secretions allowed for the metabolization of food and endocrine signaling of hunger and satiety to the brain. However, with the progressive realization that many, if not most, of the body's immune cells are associated with the gastrointestinal tract, the gut has also been ascribed a role in the organism's defense against infection. But in the light of the recently recognized importance of gut microbiota for the physiology of their multicellular hosts, it is to be expected that this will not only lead to a reconsideration of the gut's functions and that of the local endocrine, immune and nervous systems, but also to an increased interest in local neuroendocrine-immune interactions in the gut.

Another, somewhat related, lesson is that many regulatory processes in biology are functionally redundant to some extent. Thus, it is important to keep in mind that a regulatory response that seems to be top-down in the sense that it involves entities at a perceived higher level of organization influencing lower-level entities does not exclude other forms of regulation. For example, in terms of neuroendocrine-immune interactions, the pro-inflammatory cytokine interleukin-1 had been shown in the 1980s to activate the HPA-axis both at the level of hypothalamic corticotropin-releasing hormone-expressing neurons and at the level of pituitary ACTH-producing endocrine cells. Both sites of action of interleukin-1 can, in turn, give rise glucocorticoid release from the adrenal. However, in the first decade of the 21st century, it was shown that interleukin-1 can act directly on the adrenal to promote corticosteroid production (Engstrom et al., 2008). Therefore, an increase in circulating glucocorticoid concentrations under inflammatory conditions alone cannot be taken to reflect HPA-axis activation or

interaction between neuroendocrine and immune systems as such. In addition, these findings raise questions regarding the 'fine-tunedness' of these different regulatory processes and the contexts in which they are activated.

These considerations are also important to keep in mind when employing and implementing new technological approaches. For example, many 'omics' approaches, using high-throughput technologies allowing for the measurement of thousands of transcripts, proteins or metabolites, rely on the gene ontology [GO] database for interpretation of findings. However, and although "[i]deally, GO would contain a complete description of all gene functions" (Soldatos et al., 2015), Tab. 3), it has been shown regarding functional annotations "that advanced methods … significantly outperformed a straightforward application of function transfer by local [gene] sequence similarity" (Jiang et al., 2016), p. 2). Moreover, it has been proposed that "interactions between GO terms [should be] based on further experimental data that cover a wide range of biological functions," for example "using a well-recognized cell biology textbook" to gain more insight into the functional role of subcellular processes (Hansen et al., 2017), p. 2, p. 10). Such cell biology textbook-based assessment of interactions can be complemented by taking into account neuroendocrine-immune interactions of which a few were described in this chapter.

Among the new emerging approaches in science that can inform and can be informed by neuroendocrine-immune interactions are three-dimensional *in vitro* systems, such as organoids and organs on a chip. Although many of these approaches have been focused on studying interactions between cells of the same system (Morsink et al., 2020, Tambalo and Lodato, 2020), other groups have proposed three-dimensional *in vitro* systems that contain gut epithelial, immune cells and microbiota (Ambrosini et al., 2020, Li et al., 2021) or neurons, glial and endothelial cells (Chukwurah et al., 2019, Makrygianni and Chrousos, 2021). While these systems can never replace *in vivo* studies, they can be expected to prove useful in determining how neuroendocrine-immune interactions regulating bodily functions may take place at lower levels of perceived organization.

In conclusion, the, now, long histories of the neuroendocrine and immune systems and their interactions indicate that progress in our understanding occurs when conceptual and technological innovations take place and are both considered. It is hoped that this 'lesson' will carry over to the immediate future and allow for continued collective exploration of the richness of interactions between these systems and their elements in an ecologically-relevant context.

1.5. Key references

Besedovsky et al., *Journal of Immunology,* 1985. This review provides a discussion of the ways in which the immune and neuroendocrine systems can interact.
Burnet, *The Australian Journal of Science,* 1957. This historical article underlines the important conceptual work that was necessary to start and explain specific antibody production.
Guillemin, *Science,* 1978. This article contains the text of Guillemin's Nobel lecture in which he discusses the role of peptides in the brain in the context of the "new endocrinology of the neuron".
Harris, *Physiological Reviews*, 1948. This historical review lays the conceptual groundwork for how the hypothalamus influences pituitary gland hormonal secretion.
Jerne, *The EMBO Journal/Science,* 1985. This article contains the text of Jerne's Nobel lecture in which he summarizes several decades of research on specific immunity using language as a metaphor.
Pearse, *Nature,* 1976. This historical review article proposes that both peptides in the brain and intestine can function as hormones.

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