

How and why NeuroImmunology & PsychoNeuroImmunology came to be

and gave rise to neuroinflammation & immunopsychiatry



Jan Pieter Konsman
INCIA PhilInBioMed
jan-pieter.konsman@u-bordeaux.fr



History of science ... why and what?

- Why apply a historical approach to science?
 - Master the literature and honor the first investigators on a theme
 - Acquire the history of development of a technique or instrument
 - Identify origins of disciplines and approaches
 - Describe history of ideas and concepts
- What is at stake when doing history of science?
 - Technology: between poor-parent and exclusive prism
 - Education: between immersion and past of the present
 - Ideology: between conditions of possibilities and scientism
 - Epistemology: between normative and empirical

You ought to know ... important new things are happening and have been learned

- Lessons learned at the intersection of immunology and neuroscience, Steinman, J. Clin. Invest., 2012
- Mind and antibody: the return of immunopsychiatry, Ed., Lancet Psychiatry, 2015
- Neurological Disease as a Failure of Brain-Immune Crosstalk: The Multiple Faces of Neuroinflammation, Schwartz & Deczkowska, Trends Immunol., 2016
- Get It through Your Thick Head: Emerging Principles in Neuroimmunology and Neurovirology Redefine Central Nervous System “Immune Privilege”, Solomon & Rall, ACS Chemical Neuroscience, 2016

What's in a name?

Some historical (yet retrospective) affiliations

- Immunology or/and Neurology? → NeuroImmunology → Neuroinflammation
- Psychosomatic medicine → PsychoNeuroImmunology → ImmunoPsychiatry

What's in a name?

NeuroImmunology avant la lettre

- Spread bugs & antibodies to CNS
- Brain as immune-privileged organ
- Microglia as phagocytes
- Experimental Allergic Encephalomyelitis

Neuroimmunology avant la lettre

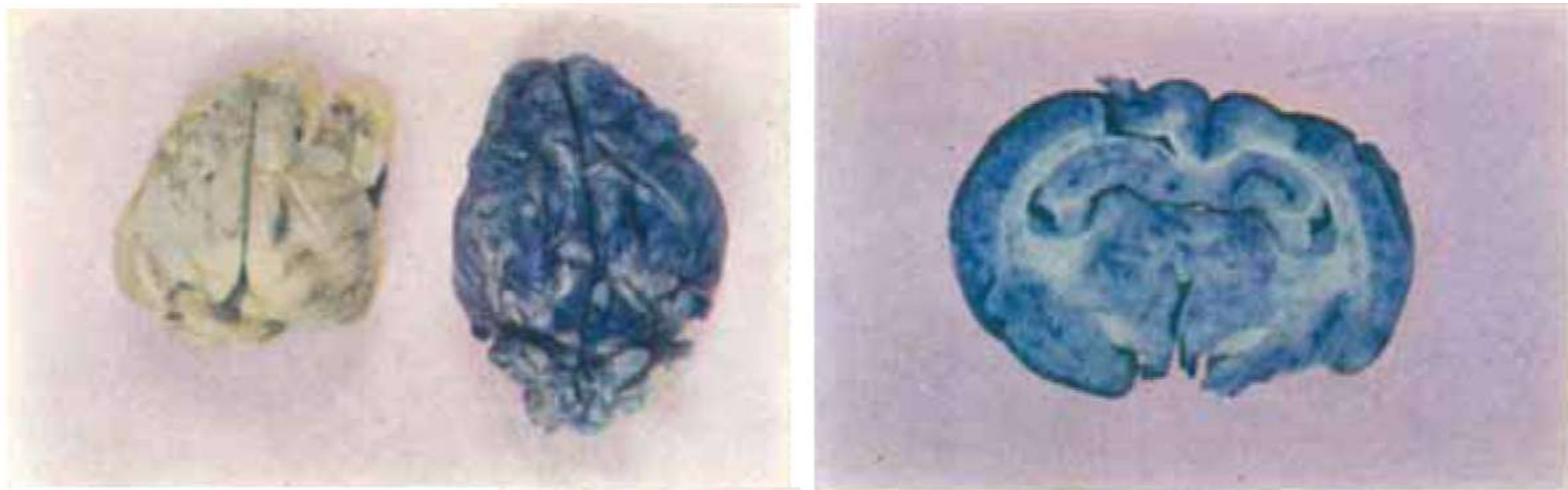
Spread bugs & antibodies to CNS (1)

- Penetration of the virus of poliomyelitis from the blood into cerebrospinal fluid, Flexner & Amoss, J. Exp. Med., 1914
- The relation of the meninges and choroid plexus to poliomyelitic infection, Flexner & Amoss, J. Exp. Med., 1917
- The passage of neutralizing substances from the blood into the cerebrospinal fluid in poliomyelitis, Flexner & Amoss, J. Exp. Med., 1917
- The passage of neutralizing substances from the blood into the cerebrospinal fluid in actively immunized monkeys, Flexner & Amoss, J. Exp. Med., 1917
- Survival of poliomyelitic virus in the rabbit brain, Amoss, J. Exp. Med., 1918
- Experiments on the nasal route of infection in poliomyelitis, Flexner & Amoss, J. Exp. Med., 1920

Neuroimmunology avant la lettre

Spread bugs & antibodies to CNS (2)

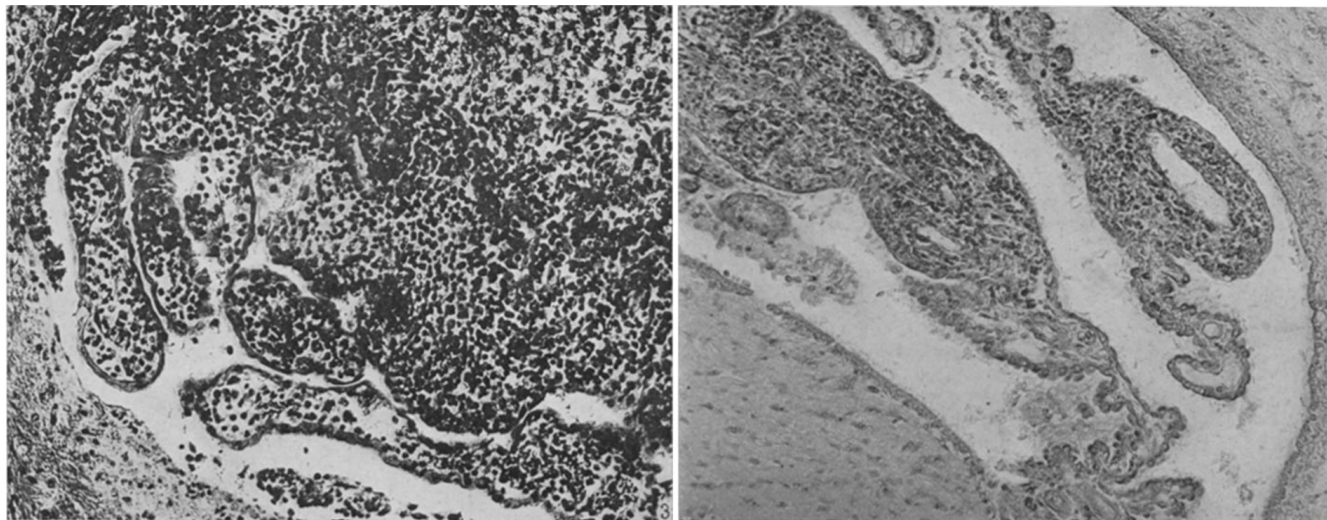
- Les rapports entre augmentation de la perméabilité de la barrière hématoencéphalique et les alteration de son substratum biologique, Stern & Rapoport, C. R. Soc. Biol., 1928
- The blood-brain barrier in infectious diseases: its permeability to toxins in relation to their electrical charges, Friedeman & Elkeles, Lancet, 1934
- The effect of bacterial pyrogen on the blood-brain barrier to trypan blue, Allen, J Pathol. Bacteriol. 1965



Neuroimmunology avant la lettre

Brain as immune-privileged organ

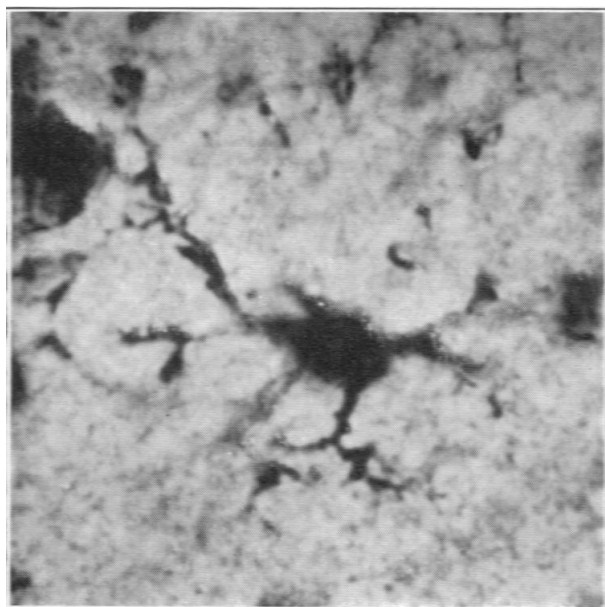
- Conditions determining the transplantability of tissues in the brain, Murphy & Sturm, J. Exp. Med., 1923
- Immunity to Homologous Grafted Skin. III. The Fate of Skin Homographs Transplanted to the Brain, to Subcutaneous Tissue, and to the Anterior Chamber of the Eye, Medawar, Brit. J. Exp. Pathol., 1948
- Immune Phenomena Elicited by Transplanted Tumors I. The Participation of the Eye and the Brain, Rambo et al., Canc. Res., 1954



Neuroimmunology avant la lettre

Microglia as phagocytes

- Studies on the Relation between Microglia, Histiocytes and Monocytes, Dunning & Furth, Am. J. Pathol., 1935
- The microglia, Rio-Hortega, Lancet, 1939
- The mononuclear phagocyte system: a new classification of macrophages, monocytes, and their precursor cells, van Furth et al., Bull. World Health Organ, 1972



Cells	Localization
PRECURSOR CELLS	bone marrow
↓	
PROMONOCYTES	bone marrow
↓	
MONOCYTES	bone marrow, blood
↓	
MACROPHAGES	connective tissue (histiocytes) liver (Kupffer cells) lung (alveolar macrophages) spleen (free and fixed macrophages) lymph node (free and fixed macrophages) bone marrow (macrophages) serous cavity (pleural and peritoneal macrophages) bone tissue (osteoclasts?) nervous system (microglial cells?)

Neuroimmunology avant la lettre

Experimental Allergic Encephalomyelitis

- Allergic encephalomyelitis in monkeys in response to injection of normal monkey cord, Morgan, J. Bacteriol., 1946
- The role of antibody in "allergic" encephalomyelitis, Thomas et al., J. Clin. Med., 1950
- Demyelination in the guinea pig in chronic allergic encephalomyelitis produced by injecting guinea pig brain in oil emulsion containing a variant of mycobacterium butyricum, Freund et al., Arch. Pathol. (Chic.), 1950
- Allergic encephalomyelitis as an experimental model for multiple sclerosis, Calif. Med., 1959
- The passive transfer of experimental allergic encephalomyelitis and neuritis with living lymphoid cells, Astrom & Waksman, J. Bacteriol. Pathol., 1962

What's in a name?

NeuroImmunology as immunology in CNS & PNS

- More than, fifty years ago it was realized that certain **neurological disorders were related to allergic reactions** and thus attention was drawn to the role of immunological factors. Since then, it has been shown that immunological mechanisms are involved not only in a growing number of disease processes of the nervous system, but also in the **development of nervous tissue**. ... Thus, with the continuing and intensive application of **immunological techniques** to the neurological sciences, **the specialty of neuroimmunology has evolved**. (Raine & Behan, J. Neuroimmunol., 1981)
- The **nervous system and the immune system interface** at a variety of levels to create the discipline that has been termed **neuroimmunology**. Neuroimmunology I: Immunoregulation in Neurological Disease, (Weiner & Hauser, Ann. Neurol., 1982)

What's in a name?

NeuroInflammation as characteristic of ...

- Inflammation in brain tissue takes a different form from that normally seen in other tissues. ... V. Hugh Perry (University of Oxford, UK) showed that lipopolysaccharide (LPS), a major inducer of the inflammatory response in most organs, causes a **marked inflammatory response in the meninges and choroid plexus without recruitment of inflammatory cells to the parenchyma** until several days after administration. (Rosenberg, Mol. Med. Today, 1997)
- In the past two decades, our understanding of the CNS has been **transformed from one of an immune-privileged site, to one where immune and inflammatory processes are pathognomic** for some of the most prevalent and tragic neurological disorders and neurodegenerative diseases. (Emmerling & Barnum, Inflamm. Res., 1997)

In the name of ...

What may have been lost along the way (1)

- If neuroimmunology as a name seems to well accommodate the privileged status of the brain with respect to immune responses, this may be less the case for neuroinflammation as a term.
- Richness and complexity of a set of biological responses reduced to one or two cellular or molecular entities:
 - Alterations in immune cells and mediators in the brain: it's not always neuroinflammation! Estes & McAllister, Brain Pathol., 2014
- Diversity and heterogeneity of molecular profiles of “glia” in brain diseases:
 - Should We Stop Saying 'Glia' and 'Neuroinflammation'? Masgrau et al., Trends Mol. Med., 2017
- How can neuroinflammation as a concept have grown from a descriptive entity specific to some conditions to something that is regularly invoked to be causal in so many different conditions?

What's in a name?

Some historical (yet retrospective) affiliations

- Immunology or/and Neurology? → NeuroImmunology → Neuroinflammation
- Psychosomatic medicine → PsychoNeuroImmunology → ImmunoPsychiatry

What's in a name?

Psychosomatic

- I have tried to present in this section some of the historic antecedents as well as the core meaning of the connotation of the word "psychosomatic," which I propose to call "**holistic**."
- The second core connotation of the term "psychosomatic" may be referred to as equivalent to "**psychogenic**," in the sense that it implies an etiologic hypothesis about the role of psychologic factors in human disease.
- Indeed, the entire notion of **psychogenesis, one incompatible with the currently prevailing doctrine of multicausality of disease**, is no longer tenable, hence, the psychogenic connotation of the word "psychosomatic" should be explicitly discarded. As one writer put it succinctly, "**To equate psychosomatic with psychogenetic is indeed pointless and obsolete**" (62).

What's in a name?

PsychoNeuroImmunology avant la lettre

- Conditioning of immune responses
- Immune alterations in mental disorders
- Effects psychological stress on immune system

Psychoneuroimmunology avant la lettre

Conditioning of immune responses

- Rôle des réflexes conditionnels dans la formation des anticorps, Metalnikov & Chorine, C. R. Soc. Biol., 1928
- Conditioning of allogeneic mice with crude and purified H-2 extracts, alone and combined with cyclophosphamide, for skin graft prolongation, Halle-Pannenko et al, Transplant. Proc., 1971
- Behaviorally conditioned immunosuppression, Ader & Cohen, Psychosom. Med., 1975
- Conditioned suppression of a thymus-independent antibody response, Cohen et al., Psychosom. Med., 1979

Psychoneuroimmunology avant la lettre

Immune alterations in mental disorders

- Pseudoallergic schizophrenia: a new clinical entity, Abrahamson, Ann. Allergy, 1959
- Schizophrenia as an immunologic disorder. I. Demonstration of antibrain globulins by fluorescent antibody techniques, Heath & Krupp, Arch. Gen. Psychiatry, 1967
- Schizophrenia: evidence of a pathologic immune mechanism, Heath, Proc. Annu. Meet. Am. Psychopathol. Assoc., 1969
- Secondary immune response to tetanus toxoid in psychiatric patients, Solomon et al., J. Psychiatr Res. 1970
- Cell-mediated immunity to human myelin basic protein in schizophrenic patients, Kuritzky et al., J. Neurol. Sci, 1976

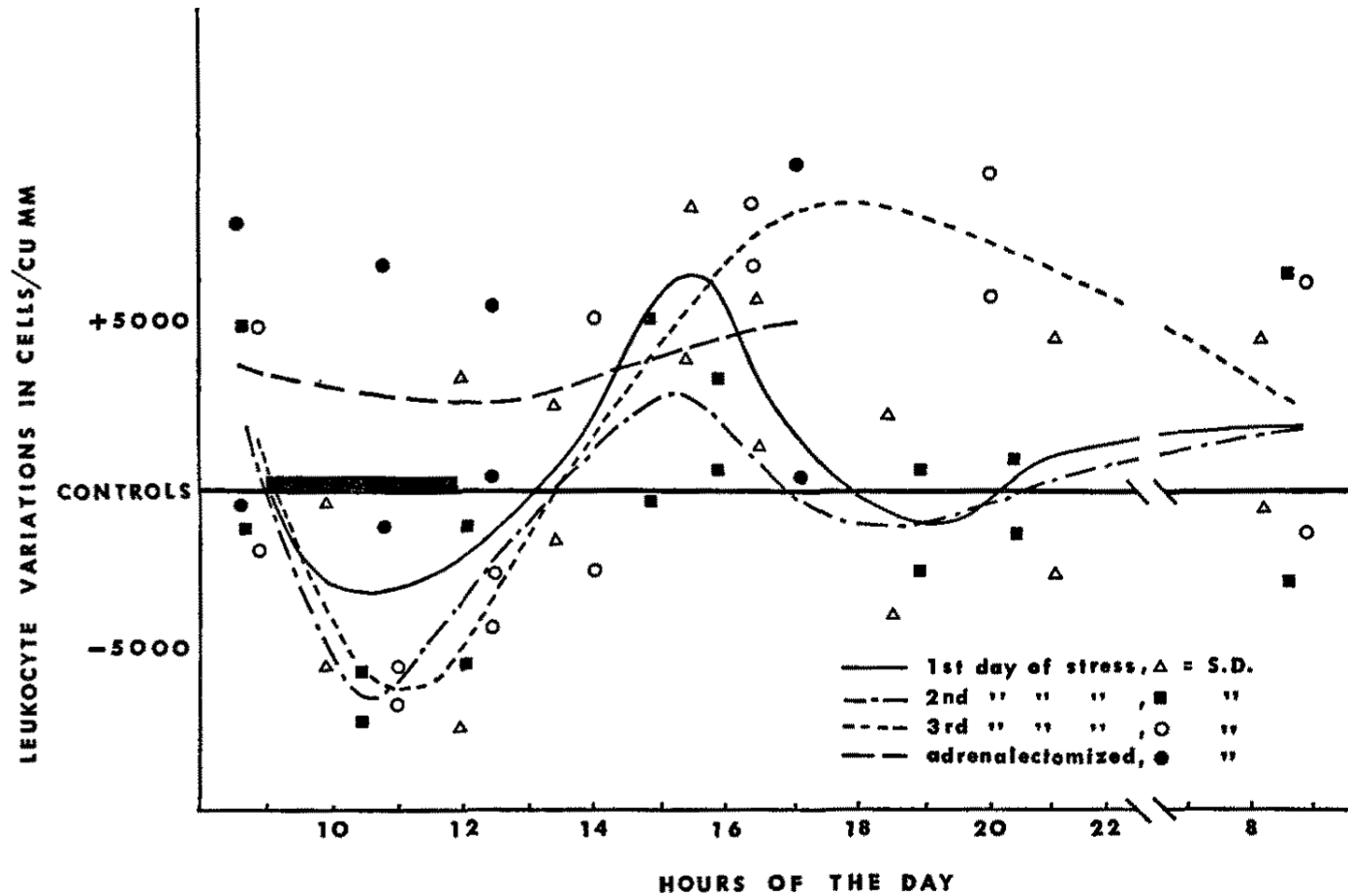
Psychoneuroimmunology avant la lettre

Effects psychological stress on immune system

- Response of circulating eosinophils to nor-epinephrine, epinephrine and emotional stress in humans, Humphreys & Raab, Proc. Soc. Exp. Biol. Med., 1950
- The effect of mental stress on the eosinophil leucocyte count in man, Kerr, Q. J. Exp. Physiol. Cogn. Med. Sci., 1956
- Response of adrenals, thymus, spleen and leucocytes to shuttle box and confinement stress, Marsh & Rasmusen, Proc. Soc. Exp. Biol. Med., 1960
- Stress and susceptibility to viral infection. I. Response of adrenals, liver, thymus, spleen and peripheral leukocyte counts to sound stress, Jensen & Rasmusen, J. Immunol., 1963
- Immunity, emotions and stress with special reference to the mechanisms of stress effects on the immune system, Solomon et al., Psychother. Psychosom., 1974

Psychoneuroimmunology avant la lettre

Effects psychological stress on immune system



What's in a name?

PsychoNeuroImmunology: psycho → immuno

- ..., “psychoneuroimmunology”² has been used to refer to studies of the **neuroendocrine mechanism mediating the effects of behavior on immune function** – and vice versa.
- In an attempt to account for such phenomena, it is quite reasonable, then, to hypothesize that changes in immune function may mediate the **effects of psychosocial factors on** the development and/or progression of some **pathophysiological states**. Such a **hypothesis is tenable**, however, only if it **can be shown that the CNS plays some role in the modulation of immunity**.

What's in a name?

ImmunoPsychiatry: immuno → psycho

- *Psychoneuroimmunology* originally ... an emphasis on the notion that psychological and neural phenomena can influence the immune system.³
- In the 1990s, two factors drove a conceptual shift in the field that led to the reversal of the hierarchy between the brain and the immune system.
 - First, studies using animal models showed clear molecular mechanisms by which immune activation leads to behavioural changes, especially changes resembling depressive symptoms;⁸
 - and, second, clinical studies showed that patients exposed to cytokine therapies for cancers or chronic viral hepatitis develop depressive symptoms and other psychiatric adverse effects.⁹
- The introduction of the term **immunopsychiatry** has created the opportunity of managing psychiatric disorders through **novel treatment approaches targeting the immune system.**

In the name of ...

What may have been lost along the way (2)

- Normal physiology and behavior:
 - The physiological (fever) and behavioral changes (reduced food intake) induced by immune activation can above all be considered adaptive and regulated responses.
- Downward (top-down) causation:
 - Fever, once established through upward causation, can, as a system's property, exert downward causation, for example on bacterial replication and certain immune responses.
- Why have pathological conditions and upward (bottom-up) explanations been favored as of lately in psychoneuroimmunology up to a point to give rise to immunopsychiatry?

What's in a name?

- History: Immunology or/and Neurology? → NeuroImmunology
→ Neuroinflammation
 - History: Psychosomatic medicine → PsychoNeuroImmunology
→ ImmunoPsychiatry
- Future: Neuroinflammation & ImmunoPsychiatry, a happy marriage of reason or a dangerous liaison?

The ambiguous relationship of science & medicine with philosophy and history of science & medicine

- Rather sloppy use of definitions and citations in science and medicine
- Scientists and clinicians self-declaring paradigm shifts or how Thomas Kuhn became the most cited historian of science
- Trading zones may better describe forces at work in interdisciplinary research fields

The ambiguous relationship of science & medicine with philosophy and history of science & medicine

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Paradigm shift announcements

PsychoNeuroImmunology, ImmunoPsychiatry

- ..., it is argued that much can be learned by reflecting on the progression of models, or "**paradigm-shifts**", It is argued, finally, that, with the emergence of behavioural medicine, and, more particularly, **psychoneuroimmunology**, ..., one can see **a new conceptualization** of the human body beginning to take shape. (Levin & Solomon, J. Med. & Phil., 1990).
- This **paradigm shift** in the study of immunoregulatory processes and the elaboration of the mechanisms underlying behaviorally induced alterations of immune function promise a better understanding and a **new appreciation of the multi-determined etiology of pathophysiological states**. (Ader, Eur. J. Pharmacol., 2000)
- Gaining a better understanding of the **role of immune system could be paradigm changing for psychiatry**. (Khandaker et al., Pscyhol. Med., 2017).

The ambiguous relationship of science & medicine with philosophy and history of science & medicine

- Rather sloppy use of definitions and citations in science and medicine
- Scientists and clinicians self-declaring paradigm shifts or how Thomas Kuhn became the most cited historian of science
- Trading zones/repertories may better describe forces at work in interdisciplinary/multidisciplinary research fields

Trading zones in science

Interdisciplinary research

- What we have are quasi-stable scientific subcultures (roughly shared ways of handling practices with their attendant values, symbols, and meanings). Above all, **we need to know how these scientific subcultures connect to each other, to the surrounding world, and to change.**
- The point of emphasizing the power of what goes on in the trading zone is that the **trading zone is not “mere mortar” between the solidity of bricks.** What is **exchange work today may well become the disciplinary pillars** of tomorrow: science is forever in flux, not just in its results but in the contours of its disciplines.
- But the necessary condition for a trading zone is that **practices** (and their interpretations) **tend to travel in packs** rather than along arbitrarily combined trajectories. These “packs” might be a set of affiliated experimental procedures Here they are tactics, there they are strategies — but also regulative values.

Trading zones in science

Interdisciplinary research

- Galison's supposed resolution to the general problem was to posit the existence of in-between languages ... which developed to enable 'trade' to happen between communities with **radically different languages**.
- His paradigm case was the invention of **biochemistry** which grew out of the invention of a **new language** which captured the appropriate parts of the language of chemistry and the language of biology.
- **Multi-disciplinarity is an extension of the specified deliverable model**. It differs from **interdisciplinarity because there is no attempt at common understanding** by either home group or foreign group – indeed, it is not clear if there is a 'home' group.

Repertories in science

Multidisciplinary research

- The framework centers on the notion of a **research repertoire**, which encompasses well-aligned **assemblages of the skills, behaviors, and material, social, and epistemic components** that a group may use to **practice certain kinds of science**, and whose enactment affects the methods and results of research.
- This account provides an **alternative to the idea of Kuhnian paradigms** for understanding scientific change in the following ways:
 - 1) it does not frame change as primarily generated and shaped by theoretical developments, but rather **takes account of administrative, material, technological, and institutional** innovations ...;
 - 2) it thus allows for tracking of the **organization, continuity, and coherence** in research practices which Kuhn characterized as '**normal science**' ...; and
 - 3) it requires particular attention be paid to the **performative aspects of science**, whose study Kuhn pioneered but which he did not extensively conceptualize.