La Seconde Guerre Mondiale

La Science Biomédicale Qui Sauve

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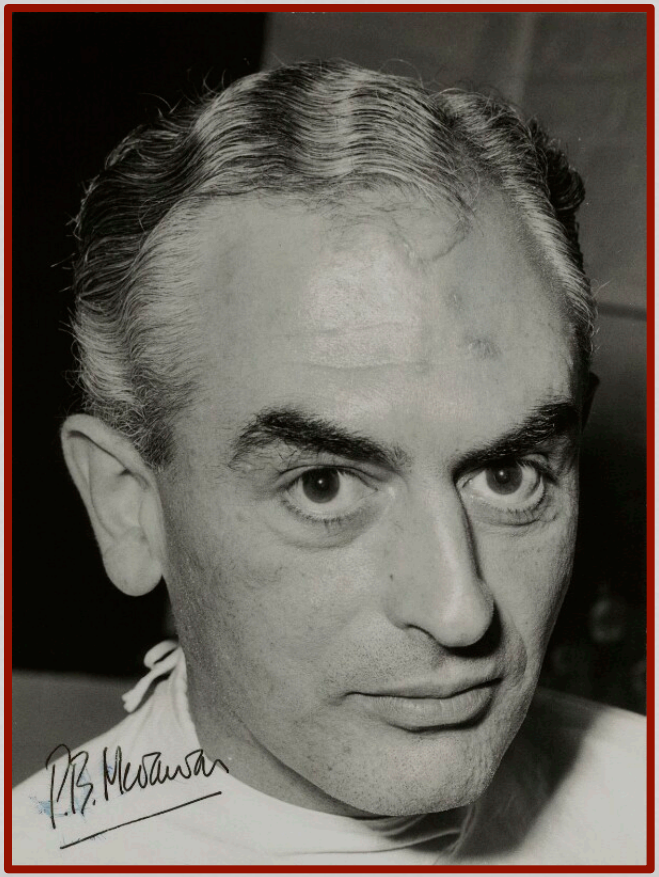
LIÈGE université
GIGA institute

Espace Universitaire de Liège – 5 février 2019

Plan de la conférence

1. Peter Medawar et les premiers pas de la transplantation d'organes.
2. Découverte de la pénicilline.
3. Progrès de la vaccination.
4. Autres découvertes : Vitamine C et DDT.
5. Conclusion générale.

1. Les premiers pas de la transplantation Peter MEDAWAR (1915-1987)



Tolérance immunitaire ACQUISE

The Journal of Immunology

No. 4379 October 3, 1953 NATURE 603

'ACTIVELY ACQUIRED TOLERANCE' OF FOREIGN CELLS

By Dr. R. E. BILLINGHAM*, L. BRENT and Prof. P. B. MEDAWAR, F.R.S.

Department of Zoology, University College, University of London

THE experiments to be described in this article provide a solution—at present only a 'laboratory' solution—of the problem of how to make tissue homografts immunologically acceptable to hosts which would normally react against them. The principle underlying the experiments may be expressed in the following terms: 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. If, for example, a foetal mouse of one inbred strain (say, *CBA*) is inoculated *in utero* with a suspension of living cells from an adult mouse of another strain (say, *A*), then, when it grows up, the *CBA* mouse will be found to be partly or completely tolerant of skin grafts transplanted from any mouse belonging to the strain of the original donor.

This phenomenon is the exact inverse of 'actively acquired immunity', and we therefore propose to describe it as 'actively acquired tolerance'. The distinction between the two phenomena may be made evident in the following way. If a normal adult *CBA* mouse is inoculated with living cells or grafted with skin from an *A*-line donor, the grafted tissue is destroyed within twelve days (see below). The effect of this first presentation of foreign tissue in adult life is to confer 'immunity', that is, to increase the host's resistance to grafts which may be transplanted on some later occasion from the same donor or from some other member of the donor's strain. But if the first presentation of foreign cells takes place in foetal life, it has just the opposite effect: resistance to a graft transplanted on some later occasion, so far from being heightened, is abolished or at least reduced. Over some period of its early life, therefore, the pattern of the host's response to foreign tissue cells is turned completely upside down. In mice, it will be seen, this inversion takes place in the neighbourhood of birth, for there is a certain "null" period thereabouts when the inoculation of foreign tissue confers neither tolerance nor heightened resistance—when, in fact, a 'test graft' transplanted in adult life to ascertain the host's degree of immunity is found to survive for the same length of time as if the host had received no treatment at all.

Earlier Work

The literature of experimental embryology is rich in evidence that embryos are fully tolerant of grafts of foreign tissues. It is less well known (though no less firmly established) that embryonic cells transplanted into embryos of different genetic constitutions may survive into adult life, although their hosts would almost certainly have rejected them if transplantation had been delayed until after birth. The transplantation of embryonic melanoblasts† provides the most conspicuous evidence of this phenomenon—not because melanoblasts are peculiar in their immunological properties, but simply because their genetic origins are at once betrayed by the pigmentation of the cells into which they ultimately develop. Unfortunately, experiments with embryonic melanoblasts, having been done with quite different purposes in mind, do not make it possible to decide whether survival into adult life is due to an antigenic adaptation of embryonic cells which have been obliged to complete their development in genetically foreign soil, or whether it is due to a suppression or 'paralysis'" of the host's immunological response.

An exactly comparable phenomenon has been described by Owen', who found that the majority of dizygotic cattle twins are born with, and long retain, red blood cells of dizygotic origin: each calf contains a proportion of red cells belonging genetically to itself, mixed with red cells belonging to the zygote lineage of its twin. There is no reason to doubt that this is because the cattle twins, being synchorial, exchange blood in foetal life through the anastomoses of their placental vessels. (This is not a peculiarity of cattle, for a human twin with red cells of dizygotic origin has lately been described'.) Inasmuch as the provenance of the red cells was revealed by their reactions with specific agglutinins, it is most unlikely that the survival of foreign erythrocyte-forming cells into adult life was made possible by any kind of antigenic adaptation. Moreover, we have found that the majority of cattle twins at birth and for long after are fully tolerant of grafts of each other's skin'. Being freshly transplanted, these grafts can have had no opportunity to 'adapt' themselves antigenically to foreign hosts, but they survived nevertheless.

The experiments of Cannon and Longmire' have a direct bearing on the phenomenon of actively acquired tolerance. About 5–10 per cent of skin grafts exchanged between pairs of newly hatched chicks of different breeds are tolerated and survive into adult life; but the percentage of successes falls rapidly as the age at which the chicks are operated increases, and reaches zero by the end of the second week. These results will be referred to later.

Experiments with Mice

A single experiment will be described in moderate detail: the recipients were mice of *CBA* strain, the donors of *A* strain. The data for transplantations between normal mice of these strains are as follows. The median survival time of *A*-line skin grafts transplanted to normal *CBA* adults (regardless of differences of sex, or of age within the interval 6 weeks–6 months) is 11·0 ± 0·3 days'. In resisting against such a graft, the host enters a state of heightened resistance; a second graft transplanted up to sixty days after the transplantation of the first survives for less than six days, and immunity is still strong, though it has weakened perceptibly, after four months. Heightened resistance may be passively transferred to a normal *CBA* adult by the intraperitoneal implantation of pieces of lymph node excised from a *CBA* adult which has been actively immunized against *A*-line skin'.

In the experiment to be described (Exp. 73), a *CBA* female in the 15–16th day of pregnancy by a

*British Empire Cancer Campaign Research Fellow.

Démonstration d'une **tolérance** immunitaire active 'acquise' vis-à-vis de cellules étrangères après exposition de celles-ci au cours de la **vie fœtale**. Les animaux (souris, poulets) ainsi traités sont non seulement tolérants aux cellules étrangères originelles mais aussi, pendant la vie adulte, aux greffes de peau provenant du même donneur original un d'un donneur de même constitution antigénique.

Cette tolérance acquise est **spécifique**.

La tolérance acquise est l'exact contraire de l'**immunité** activement acquise pendant la vie adulte;

Prix Nobel 1960 de physiologie ou médecine *pour leur découverte de la tolérance immunitaire acquise*

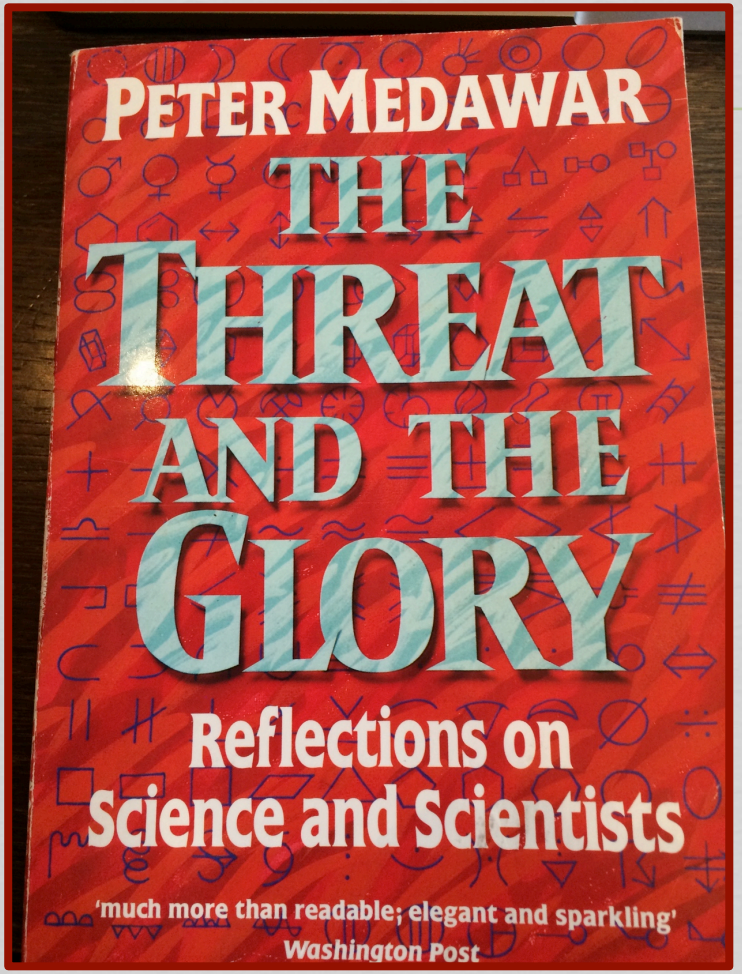
Peter Medawar et Frank Macfarlane Burnet (1960)

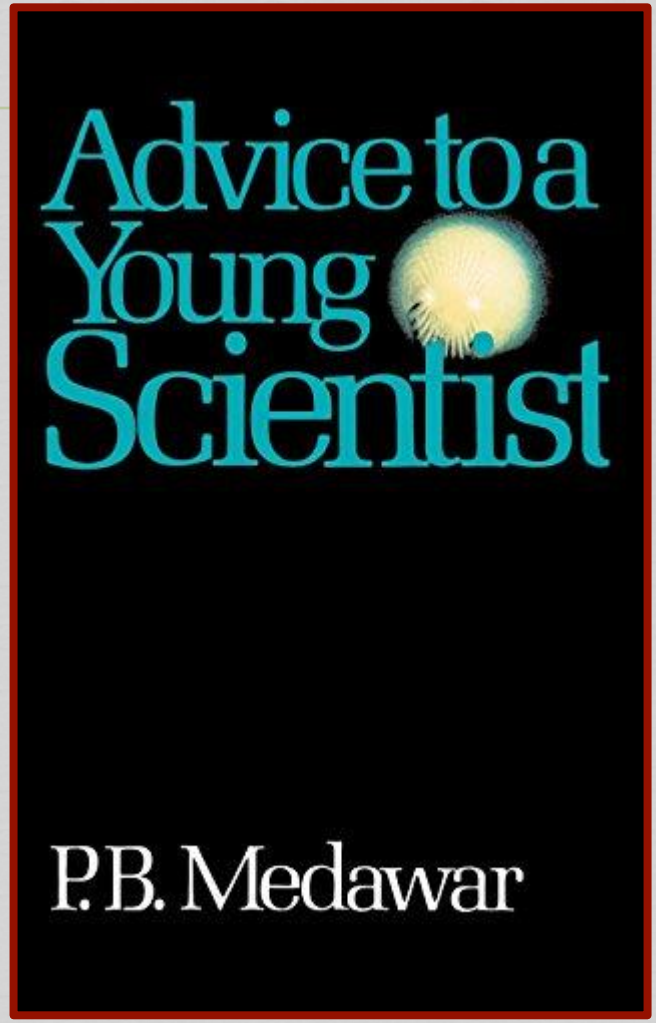
« Nous devons considérer la présence de lymphocytes dans le thymus comme un accident de l'évolution sans grande importance. »

Sir Peter MEDAWAR (1964)

« Si, comme je le pense, le thymus est le site où se déroulent la prolifération et la différenciation de lymphocytes dotés de fonctions immunologiques précises, nous devons aussi lui attribuer une autre fonction – l'élimination ou l'inhibition de lymphocytes réactifs vis-à-vis du Soi. »

Frank MacFarlane BURNET, Université de Londres (1962)


PETER MEDAWAR
THE THREAT AND THE GLORY
Reflections on Science and Scientists
'much more than readable; elegant and sparkling'
Washington Post


Advice to a Young Scientist
P.B. Medawar

Transplantations d'organes

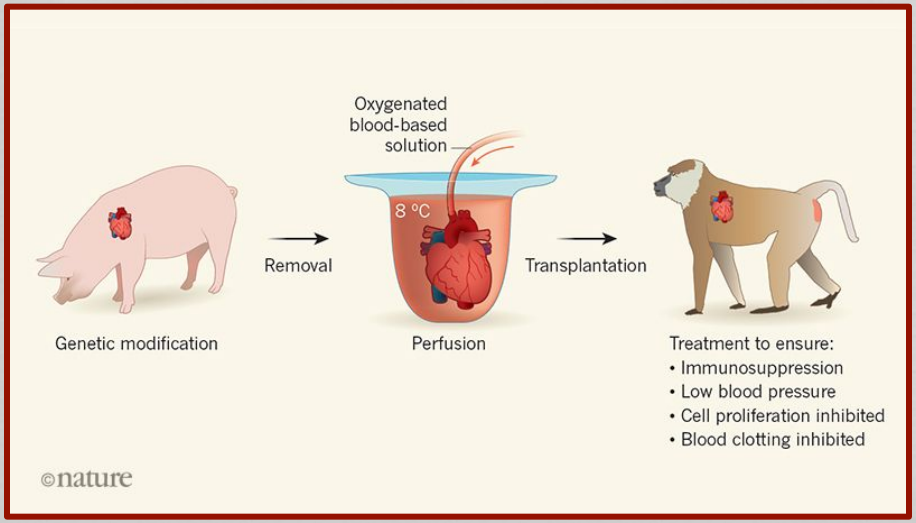
Statistiques des transplantations au CHU de 1983 à 2018 :

- 392 greffes de **cœur**
- 741 greffes de **foie**
- 1.280 greffes de **rein**
- 69 greffes de **pancréas + rein**
- 2 greffes d'**intestin**
- ± 100 greffes/an de **cellules souches hématopoïétiques**.

Centre Inter-universitaire de Recherche en Xénotransplantation (CIREX)

CIREX (1994-1999)

- Faculté de Médecine vétérinaire
- Service de Chirurgie de transplantation (CHU)
- Service d'Anesthésiologie (CHU)
- Service d'Hématologie (CHU)
- Centre d'Immunologie de Liège (CIL)



XENOTRANSPLANTATION 1996; 3:296–303
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XENOTRANSPLANTATION
ISSN 0908-665X

Development of thymus autografts under the kidney capsule in the pig: A new "organ" for xenotransplantation

Lambrigts D, Franssen C, Martens H, Van Calster P, Meurisse M, Geenen V, Charlet-Renard C, Dewaele A, Coignoul F, Lamy M, Alexandre GPJ. Development of thymus autografts under the kidney capsule in the pig: A new "organ" for xenotransplantation. Xenotransplantation 1996; 3:296–303. © Munksgaard, Copenhagen

Abstract: Ten piglets, 7 to 16 weeks old, were partially thymectomised and 1 to 4 cm^3 of minced thymic fragments autografted under the renal capsule. They were sacrificed, respectively, after 2, 4, 6, 8, 12, and 20 weeks. After 2 weeks, irregular whitish zones are present under the renal capsule. They were composed principally of two cell types: the first type was characterized by small round basophilic nuclei and little cytoplasm typical of lymphocytes; the second cell type had larger ovoid nuclei and a large vacuolised cytoplasm. Each cell type could be found in separate lobules or mixed in variable proportion in the same structure. The thymic autografts grew to form a layer up to 4 mm thick after 20 weeks. In the meantime, at the beginning of 4th week, the lobular structure became well organized with the cell type presenting large nuclei and cytoplasm being restricted to the center of the lobules while lymphocytes composed a peripheral layer. Hassal corpuscles (HC) appeared in the center of the lobules. Immunohistochemical labeling with anti-cytokeratin mono- and polyclonal Ab and with anti-neurophysin polyclonal Ab displayed all the characteristics of normal functional thymic microenvironment. It is proposed that this novel experimental preparation ending up as a neo-organ (thymo-kidney) be used for xenotransplantation in an attempt to produce specific xenotolerance.

D. Lambrigts, C. Franssen, H. Martens, P. Van Calster, M. Meurisse, V. Geenen, C. Charlet-Renard, A. Dewaele, F. Coignoul, M. Lamy, and G.P.J. Alexandre

"Centre Interdisciplinaire de Recherches en Xénotransplantation (CIREX)," University of Liège, Faculties of Medicine and Veterinarian Medicine, Boulevard de Colonster 20, 4000 Liège (Sart Tilman), Belgium

Key words: pig – baboon – xenotransplantation – thymus – tolerance

Address reprint requests to Dr. Lambrigts D, "Centre Interdisciplinaire de Recherches en Xénotransplantation (CIREX)," University of Liège, Faculty of Veterinarian Medicine, Boulevard de Colonster 20, Building 43, 4000 Liège (Sart Tilman), Belgium.

Accepted September 22, 1996.

Introduction

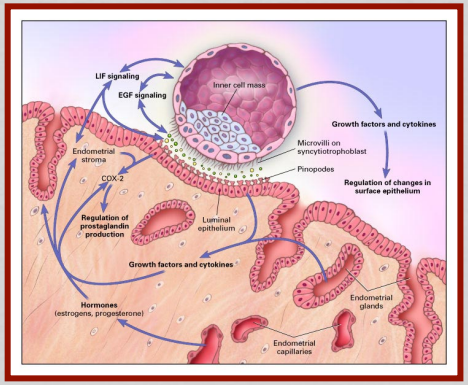
Organ transplantation has become the treatment of choice for a number of severe disorders but increasing organ shortage is depraving this modern therapeutic procedure from filling its goal. Xenotransplantation, if and when applicable, could solve most of the problems related to the present practice of organ transplantation. For several reasons, the pig represents the most valid candidate as a source of organs for human [1,2]. However, pig-to-man xenotransplantation being discordant [3], two immunological barriers need to be breached: hyperacute humoral rejection caused by natural xenoantibodies of man against antigens of the pig vascular endothelium and the more classical cellular rejection that is going to ensue. Contrarily to what was primarily thought, the latter will probably be stronger in xenografts than in allografts [4–7].

It has been shown that humoral rejection may be avoided by procedures aimed at eliminating natural antibodies responsible for hyperacute rejection of human ABO-incompatible allografts [8]. Hyperacute humoral rejection of discordant xenografts may be similarly avoided [9,10]. Moreover, the practice of ABO-incompatible allografts in man [11] taught us that a peculiar phenomenon is taking place in recipients receiving ABO-incompatible allografts, while natural antibodies against the donor's vascular endothelium return after grafting but fail to initiate humoral rejection. The name of accommodation that was given by F.H. Bach [12] to this phenomenon fits well with what we believe is the underlying process,

Le paradoxe immunologique de la grossesse
(Peter Medawar, 1953)

Grâce à la hCG (human chorionic gonadotrophin), l'embryon joue lui-même un rôle actif :

1. Dans son implantation dans l'utérus
2. Dans l'absence de son rejet (**tolérance**) par le système immunitaire de la mère
3. Dans la formation du placenta.

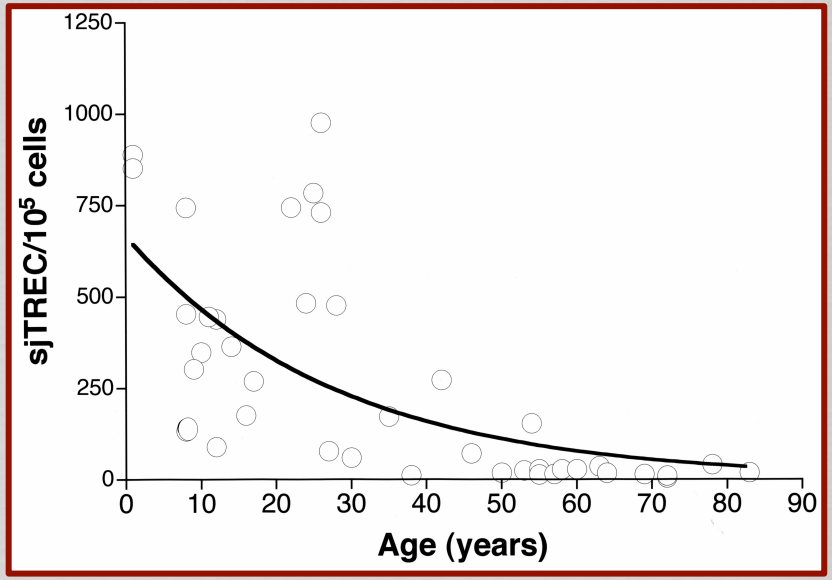


Thèses de doctorat en Sciences biomédicales et pharmaceutiques de

Sophie PERRIER d'Hauterive (CPMA), Virginie GRIDELET (CPMA) et Barbara POLESE

GIGA-I³ Immunoendocrinologie – Implantation et Tolérance de l'embryon

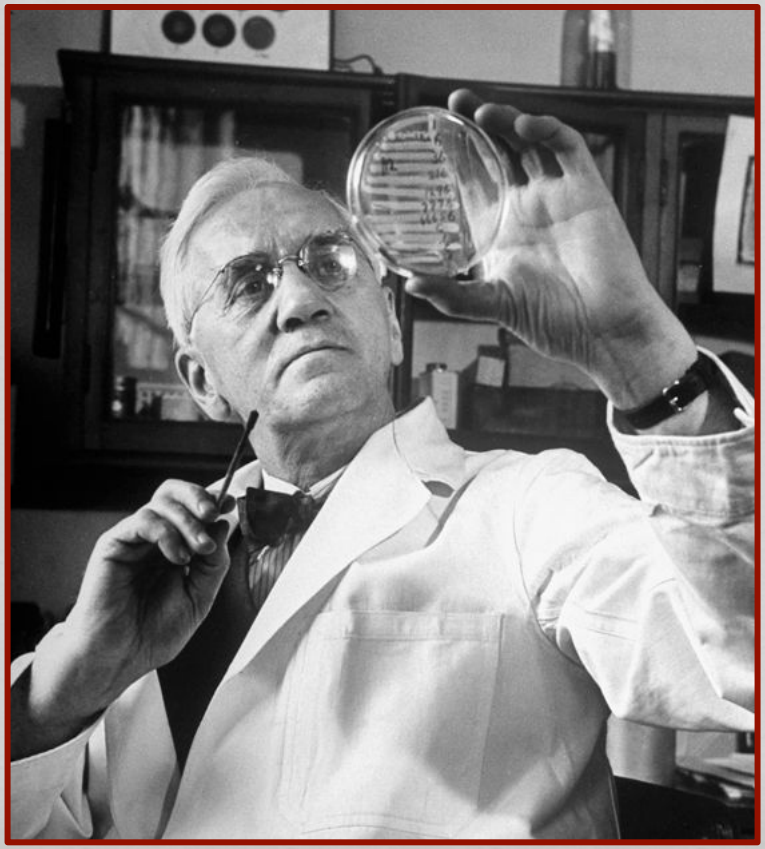
Thymus & Immunosénescence

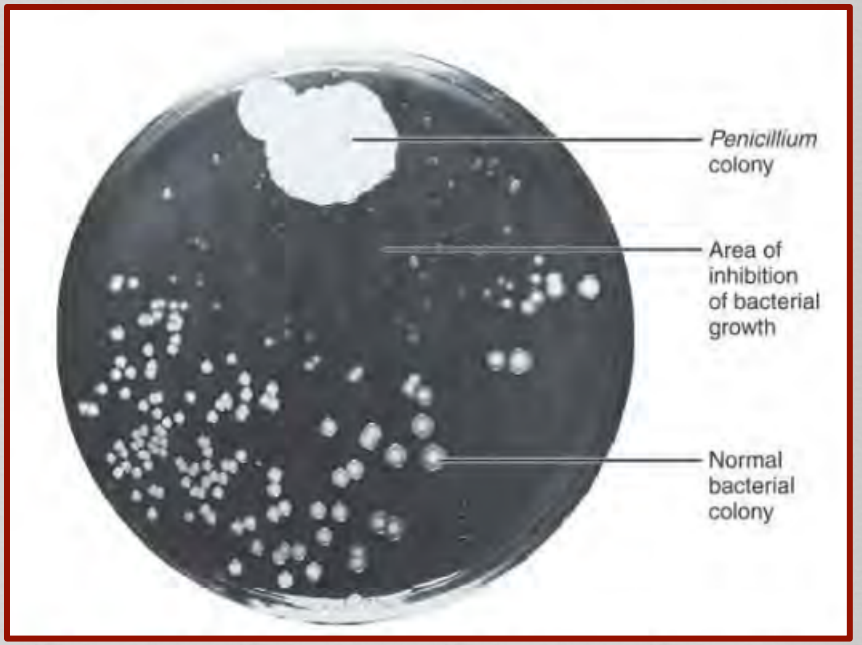


- *Plus grande susceptibilité aux infections.*
- *Moins grande efficacité de la vaccination, particulièrement contre la grippe.*
- *Diminution de l'immunité anti-tumorale.*
- *Parfois spécifiquement associé à la fragilité du grand age.*
- *Augmentation des maladies autoimmunes (controversé).*

2. Découverte de la pénicilline (1928)

Alexander FLEMING (1881 – 1955)



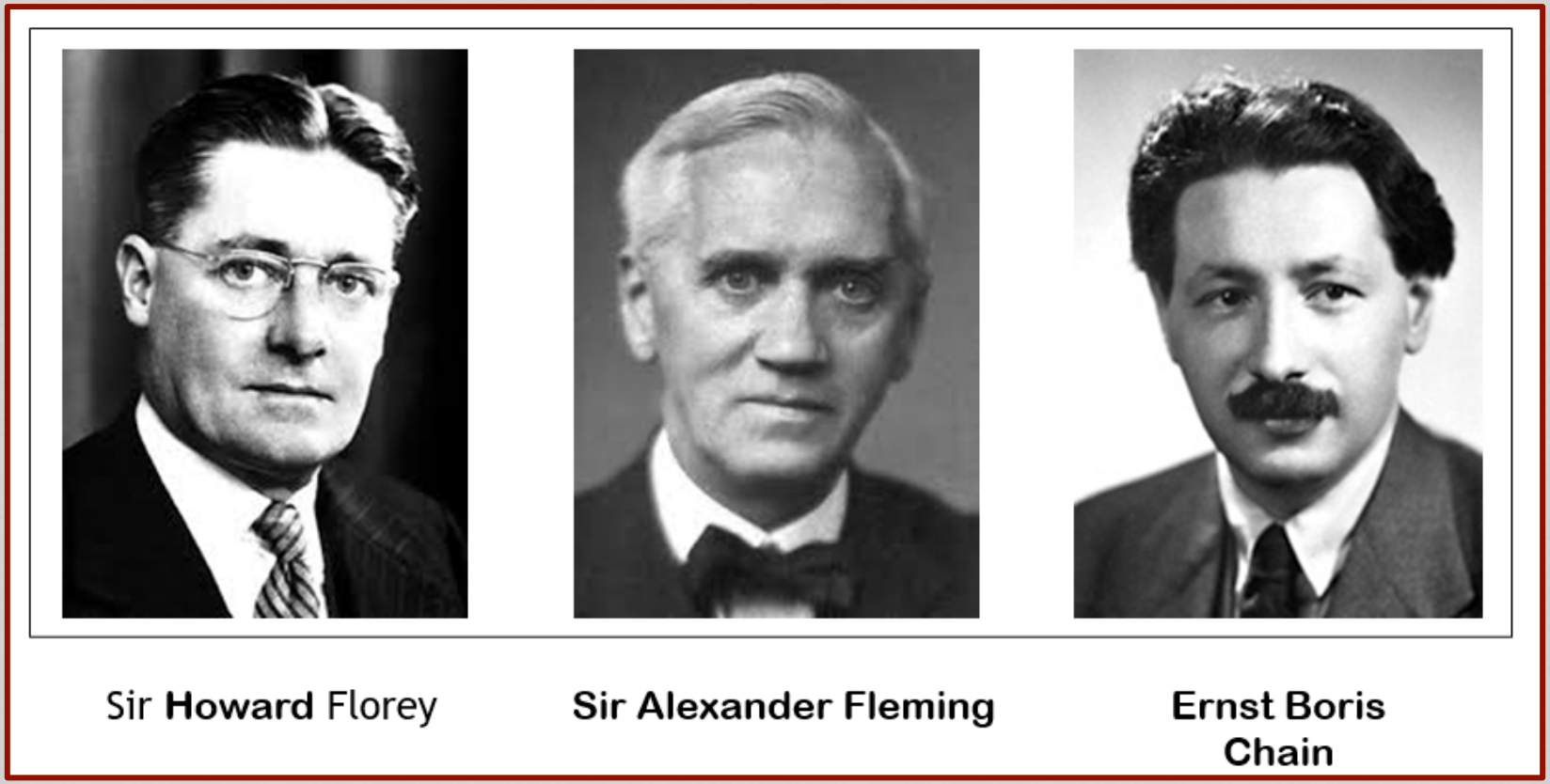


Découverte de la pénicilline (1928)

Modèle de la découverte 'accidentelle' mais, comme le disait Louis Pasteur :

« Le hasard ne favorise que les esprits préparés ».

Prix Nobel 1945 de Physiologie ou Médecine *pour la découverte de la pénicilline et de ses propriétés curatives de nombreuses maladies infectieuses*



Sir **Howard** Florey

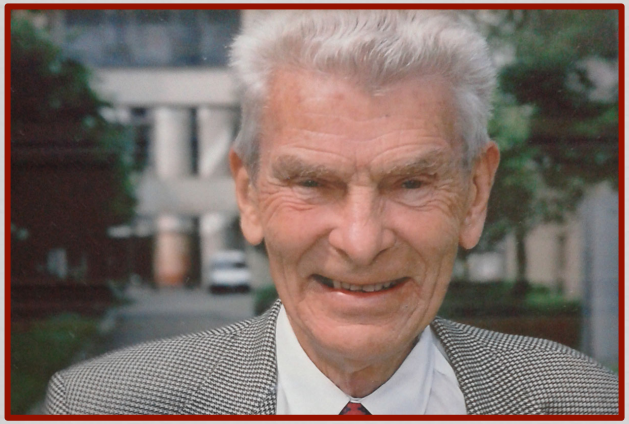
Sir Alexander Fleming

Ernst Boris Chain

« Sans Fleming, pas de Chain ni de Florey; sans Chain, pas de Florey ! »

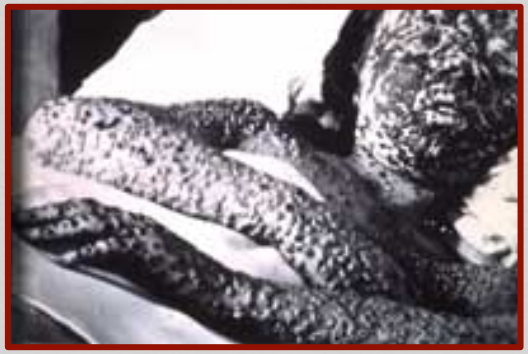
Triomphe planétaire !

La résistance aux antibiotiques

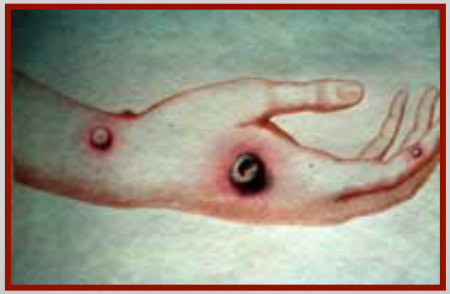


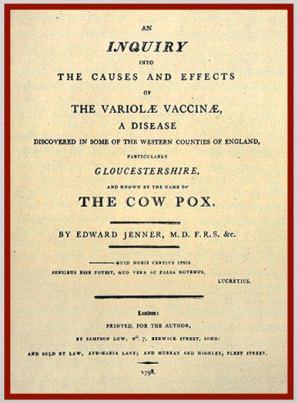
Centre d'Ingénierie des Protéines (CIP) de l'ULiège
Jean-Marie GHYSEN, Jean-Marie FRERE et Bernard JORIS

3. Les progrès de la vaccination



Edward JENNER (1749-1823)





AN

INQUIRY

INTO

THE CAUSES AND EFFECTS

OF

THE VARIOLÆ VACCINÆ,

A DISEASE

DISCOVERED IN SOME OF THE WESTERN COUNTIES OF ENGLAND,

PARTICULARLY

GLOUCESTERSHIRE,

AND KNOWN BY THE NAME OF

THE COW POX.

BY EDWARD JENNER, M.D. F.R.S. &c.

LUCRETIUS.

London:

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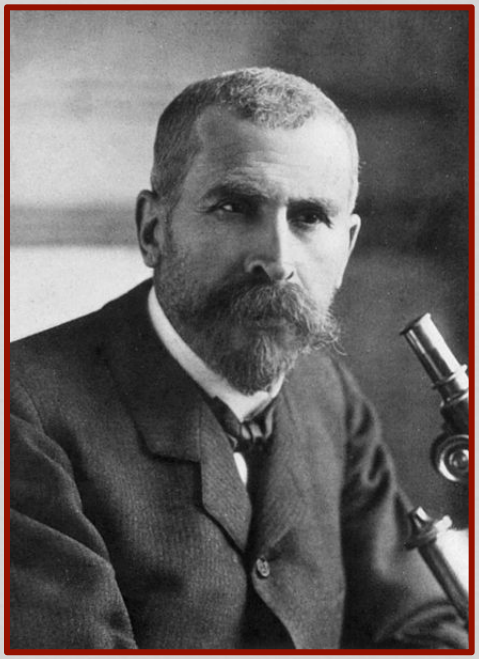
BY SAMPSON LOW, N°. 7, BERWICK STREET, SOHO:

AND SOLD BY LAW, AVE-MARIA LANE; AND MURRAY AND HIGHLEY, FLEET STREET.

1798.

L'Institut Louis Pasteur
Emile Roux & Alexandre Yersin

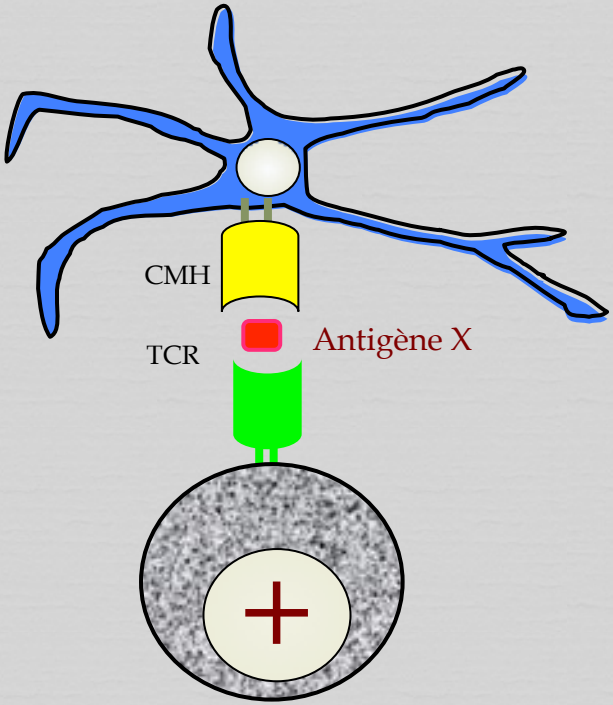


Jonas SALK (1914-1995)

Projet Win2Wal THYDIA 2019-2021

Vaccination classique

Cellule présentatrice d'antigène

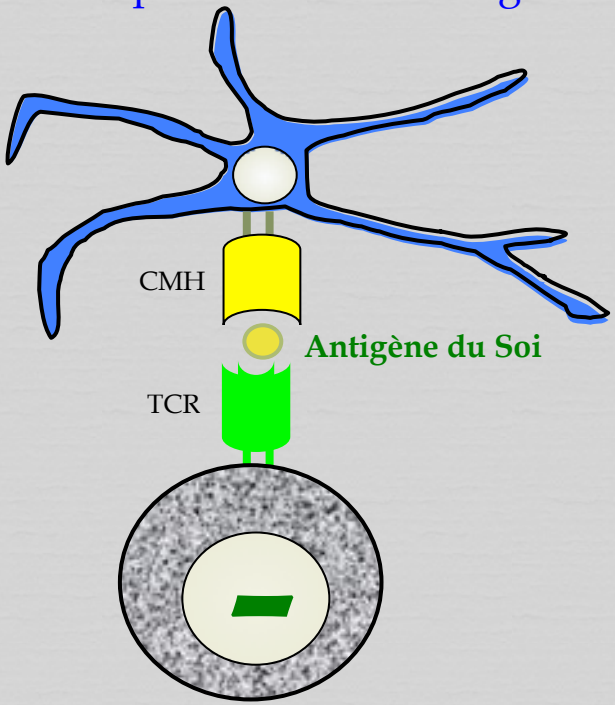


Réponse **immunogène**
Activation de cellules T naïves
Induction de cellules T mémoires

Diabète de type 1 (DT1)
Antigènes X = Insuline, GAD65,…

« Self-vaccin *contraire* contre le DT1 »

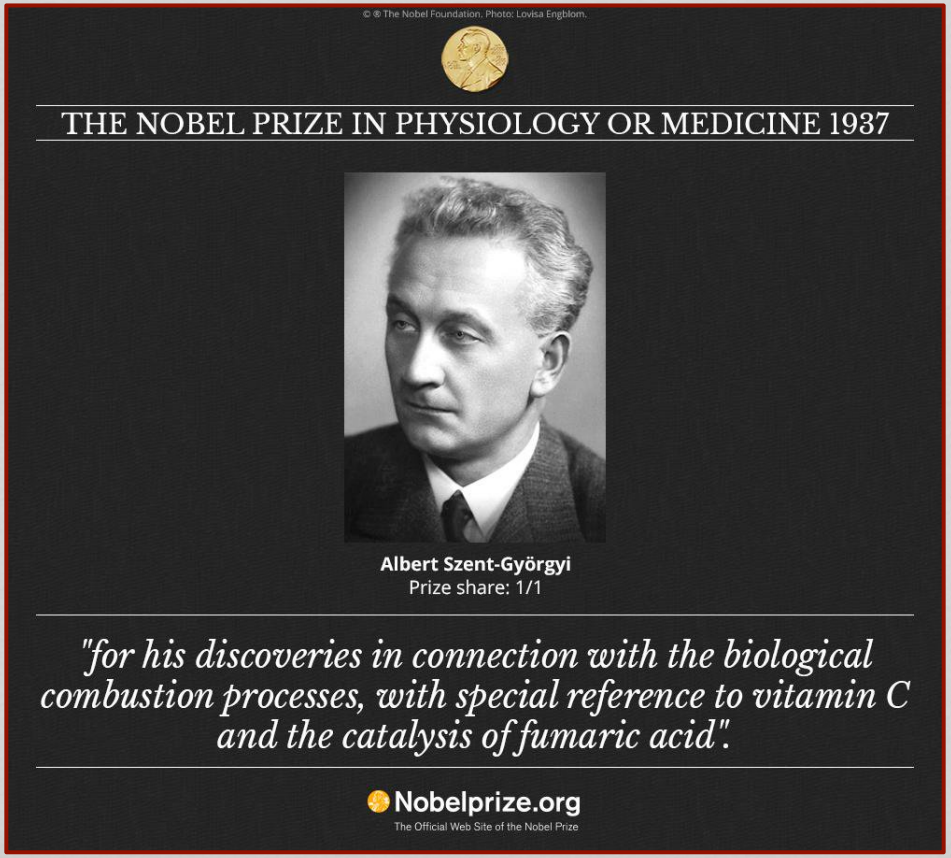
Cellule présentatrice d'antigène



Réponse **tolérogène**
Délétion des cellules T réactives au Soi
Génération de Treg spécifiques du Soi

Antigènes du Soi thymiques liés au DT1
IGF-2, GAD67

4. Autres découvertes
Vitamine C



Autres découvertes
L'insecticide DDT

Paul Hermann Müller

- Paul Hermann Müller was awarded the Nobel Prize in Physiology or Medicine in 1948 "for his discovery of the high efficiency of DDT as a contact poison against several arthropods."

L'armée américaine a utilisé massivement le DDT pour éteindre une épidémie de typhus à Naples

MAIS

- Développement de la résistance au DDT !
- Effets cancérigènes possibles.
- Toxicité pour la femme enceinte et le fœtus !
- **Premier perturbateur endocrinien !**

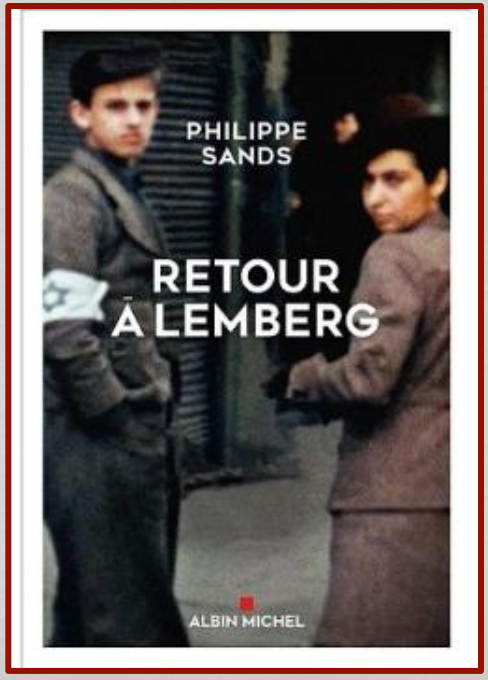
In memoriam – Jean-Pierre Bourguignon (1950-2019)

- Professeur d'Endocrinologie pédiatrique ULiège.
- Spécialiste du contrôle neuroendocrine de la puberté.
- *Prix 2014 Andrea Prader* de l'ESPE.
- Co-président de la « *Global Endocrine Disrupting Chemicals Policy Task Force* » de l'Endocrine Society (2014).
- *Outstanding Public Service Award* de l'Endocrine Society (2016).

Pr Anne-Simone PARENT

5. Conclusion générale

Les progrès de la science biomédicale n'ont rien pu faire contre la folie des hommes, le Mal Absolu, les premiers "génocide" et "crime contre l'humanité"…



Merci pour votre attention !

Pour mes 61 ans ce 6 février, j'appelle à une collecte de dons en faveur de la **Fondation Léon Fredericq**, fondation hospitalo-universitaire d'**utilité publique** *pour la recherche biomédicale liégeoise.*

IBAN BE16 2400 7780 1074

Communication libre :
Fondation Léon Fredericq – 61 ans Vincent Geenen – CC4012