Biological Evolution by marvellous Tinkering

by Bernard Swynghedauw
DM, DSc, AIHP, Emeritus Director of Research at INSERM
(National Institute of Health and Medical Research)
Corresponding Member of the National Academy of Medicine
Past-president of the Federation of European Physiological Societies (FEPS)
U342 INSERM-Hôpital Lariboisière Paris
Bernard.Swynghedauw@inserm.fr

The term "tinkering" used to characterise evolution was first proposed by François Jacob, Nobel Prize winner in Medicine, in a famous article published in the journal *Science* in 1977. Thereafter, Jacob developed this idea various times[1]. Tinkering is now a widely accepted concept, even if the term itself is not always used; the French word for tinkering is *bricolage*[2]. Jacob's article is comprised of two parts. In the first part, the author attempts to determine the boundary between scientific knowledge and more holistic knowledge which he characterises as *mythical, magical, or religious.* This debate is still ongoing, even if it is now more concerned with scientific culture and humanities. The second part of the article is devoted to tinkering which the author portrays as the driving force of evolution.

Generally speaking, it is clearly not for Jacob, a question of comparing science to tinkering in the trivial sense of the term, but rather of explaining that scientific knowledge is made up of thousands of fragmentary observations that come together to result in a discovery or innovation. This is also the case with biological evolution in the lead up to the appearance of a new trait or a new living species. In this sense, innovators are more like tinkerers than engineers;

1. Including, among others, in Patrick Tort's dictionary (Bricolage de l'évolution. *Dictionnaire du Darwinisme et de l'évolution*. Vol 1. pg 414-419. 1996 Presses Universitaires de France).
2. The concept of molecular tinkering is central to the "Guide critique de l'évolution" (edited by Guillaume Lecointre, Belin, Paris, 2009) as well as to LE Strickberger which is a bit like the Bible of the biology of evolution ("Evolution" Hall BK, Hallgrimsson B. Jones and Bartlett publishers. 4th edition, Boston 2008, see page 299 in particular). "The origins of genome architecture" by M. Lynch (Sinauer publishers, Sunderland 2007) is the benchmark for molecular evolution according to Jacob's article (page 377) by considering the concept which it covers as accepted by the vast majority of scientists. *Tinkering* is absent from the index of certain other important treatises such as "Evolution" by Ridley M (Blackwell, 3th edition, Madlen, 2005), "Evolution" by Barton NH and al. (Cold Spring Harbor 2007) or "Evolution" by Stearns SC and al. (Oxford University Press, 2d edition, 2005), but in fact, in these books, if the term "tinkering" is not used, the concept of tinkering or of imperfections remains crucial. This is also the case for Darwin himself - we will come back to this in detail later.

innovation is a discovery which generally results from an assembly of unrelated observations as opposed to a preconceived plan with a known result which is the case in the work of an engineer[3].

This article is particularly important because it is far from being theoretical. Every page is illustrated with concrete examples that make it easy to understand. This example should be followed more often.

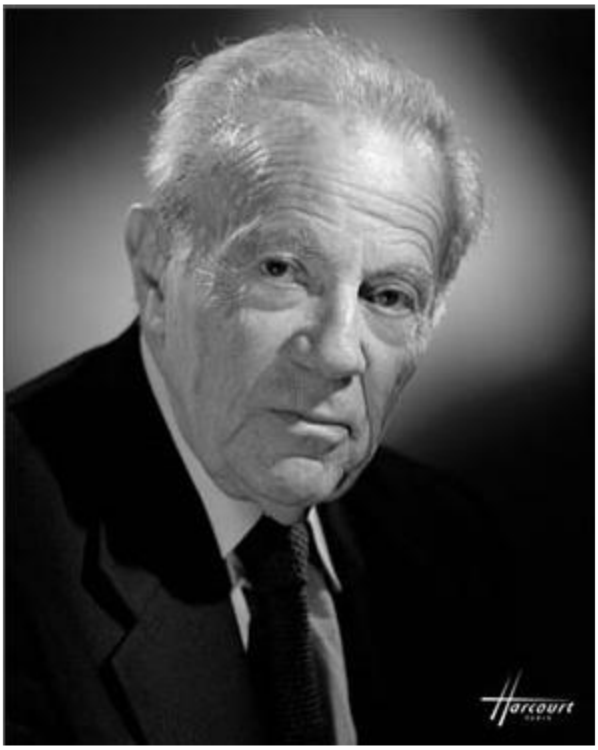

***Figure 1:* François Jacob (1920-2013)** *(photo studio Harcourt) F. Jacob was a Companion of the Liberation, Winner of the Nobel Prize in Medicine (1965, with Lwoff and Monod), member of The Academy of Science (1977) and a member of the French Academy(1996)*

SCIENTIFIC KNOWLEDGE – *1. A WORLD VIEW OF SCIENCE*

By characterising *scientific knowledge* and *magical or mythical knowledge,* Jacob brings the debate to a sudden end. Mythical or magical knowledge in the usual sense, if it is still relevant, generally concerns unscrupulous people and

3. The idea was the subject of a well-known best-seller by Steven Johnson [*Where good ideas come from. The natural history of innovation*. Riverside Books. Penguin Books. NwY. 2010] whose author also quotes Jacob (page 29). It was also taken up by journalists (such as Francis Pisani in the supplement of Le Monde. Science & Techno on the 14 January 2012). Furthermore, it is at the origin of the concept of *fablab* (contraction of the words FABrication and LABoratory) uniting engineers, computer scientists and artists with the objective of making all sorts of prototypes from extremely varied material that were almost thrown away. This "neo-artisanat" is very similar to tinkering. It is now established in the form of a *faclab* at the Université de Cergy-Pontoise [Cécile Bothorel, "Des diplômes supérieurs de bidouillage" , Le *Monde Sciences & Techno*. 25 February 2012 page 3].

causes science hardly any problems at all. However, religious knowledge is of a different nature altogether; it is of the order of faith which, by definition, belongs to a field other than science. This is even the case for the major religions who strive to reconcile them[4].

However, things are not so simple when one contrasts scientific knowledge or culture with philosophical or literary culture which are known as the "humanities". The debate was popularised by Charles Percy Snow in his book "The Two Cultures"[5]. It is currently at the heart of every educational project and underlines the all-too-frequent lack of scientific education of many philosophers[6].

The last paragraph of Darwin's *Origin of Species* (1859)

This is the last paragraph of the book. Darwin was a bit of a poet in his own way and this extract colourfully sums up how he really "saw" life:

It is interesting to contemplate a tangled bank, clothed with many plants of many kinds, with birds singing on the bushes, with various insects flitting about, and with worms crawling through the damp earth, and to reflect that these elaborately constructed forms, so different from each other, and dependent upon each other in so complex a manner, have all been produced by laws acting around us. These laws, taken in the largest sense, being Growth with Reproduction; Inheritance which is almost implied by reproduction; Variability from the indirect and direct action of the conditions of life, and from use and disuse: a ratio of Increase so high as to lead to a Struggle for Life, and as a consequence to Natural Selection, entailing Divergence of Character and the Extinction of less-improved forms. Thus, from the war of nature, from famine and death, the most exalted object which we are capable of conceiving, namely the production of the higher animals, directly follows. There is grandeur in this view of life, with its several powers, having been originally breathed by the Creator into a

---

4. The most famous attempt in France was undertaken by Teilhard de Chardin [*Œuvres* Vol. *2. L'apparition de l'homme*. Seuil publishers. Paris. 1955] and revived by a Jesuit and doctor in physics, François Euvé [F. Euvé. *Darwin et le christianisme. Vrais et faux débats*. Buchet-Chastel Paris 2009]. For many Christians, these two modes of knowledge are both different and perfectly compatible. They must oppose the radically opposing views of Richard Dawkins [*Pour en finir avec Dieu.* Perrin, Paris 2009], for whom the existence of God, is "*scientifically extremely unlikely"*.

5. C.P. Snow "*The two cultures"* (Cambridge University Press. 12th edition, 2009, the first edition was first published in 1959; an Introduction by S. Collini was added in 1964. The point of departure of this famous book was the "Rede lecture" delivered in May 1959 by Snow in the *Senate House* of Cambridge). The debate was resumed brilliantly, but in more polemical terms by J-P Dupuy ["*Mettre la science en culture",* Le Débat 2007, N° 145, 35-39]

6. Even though there are notable exceptions such as Paul Ricœur in his interview with J-P Changeux, or even Anne Fagot-Largeault in her teaching at the Collège de France. Other exceptions are Paul Rabinow or Claude Debru. The real problem with this kind of intercultural dialogue is found more at the level of training, particularly in secondary or university education, or in that provided by the media, levels where caesura is still complete.

few forms or into one; and that, whilst this planet has gone cycling on according to the fixed law of gravity, from so simple a beginning endless forms most beautiful and most wonderful have been, and are being evolved.

@@@@@@@

Firstly, let's discuss scientific knowledge or as Jacob said, the *world view of science*. The subject is particularly relevant at moments when the media seize upon the least discovery and make generalisations, often to the detriment of scientific truth. Scientific knowledge presupposes *what is possible* and is based on experiments or observations which are often repeated by thousands of research teams. These fragmentary results must be synthesised from time to time by an older, more experienced or better scientist who is even more likely to produce a broader consensus. *The invention of a possible world or of a tiny fraction of that world* ultimately remains essential.

Scientific knowledge is, in essence, fragile, controversial and the subject of much debate. However, in spite of these properties, consensus still very much exists. Who would challenge the roundness of the Earth or the fact that it revolves around the sun? Who would dare to say that smoking does not cause cancer? Who would dare to claim that an ear of corn did not come from a seed or, in spite of the problem of antibiotic resistance, that antibiotics cannot kill some germs? It is important to note that such consensus is only achieved because science

> *does not aim at reaching at once a complete and definitive explanation of the whole universe,*

even today with the powerful globalisation of science as a result of developments in technology. There are many examples of this process including the three that follow.

- *Nature*[7] recently published an extraordinary photo which was presented at the American Astronomical Society meeting in Boston on 25th May 2011. It revealed our whole universe in three dimensions in one single image; it provides us with a 3D view of 45,000 galaxies in one single projection with the furthest being situated 290 million parsecs away[8]. This kind of photomontage is the result of thousands of publications which were seemingly

7. Nature 2011, 474, 10.
8. The parsec, or parallax per second, is a unit of distance equal to 3,216 light years per second

modest in their ambition, each one only showing one or a perhaps only a few galaxies but which eventually provided us with an unrivalled view of the universe (Figure 2).

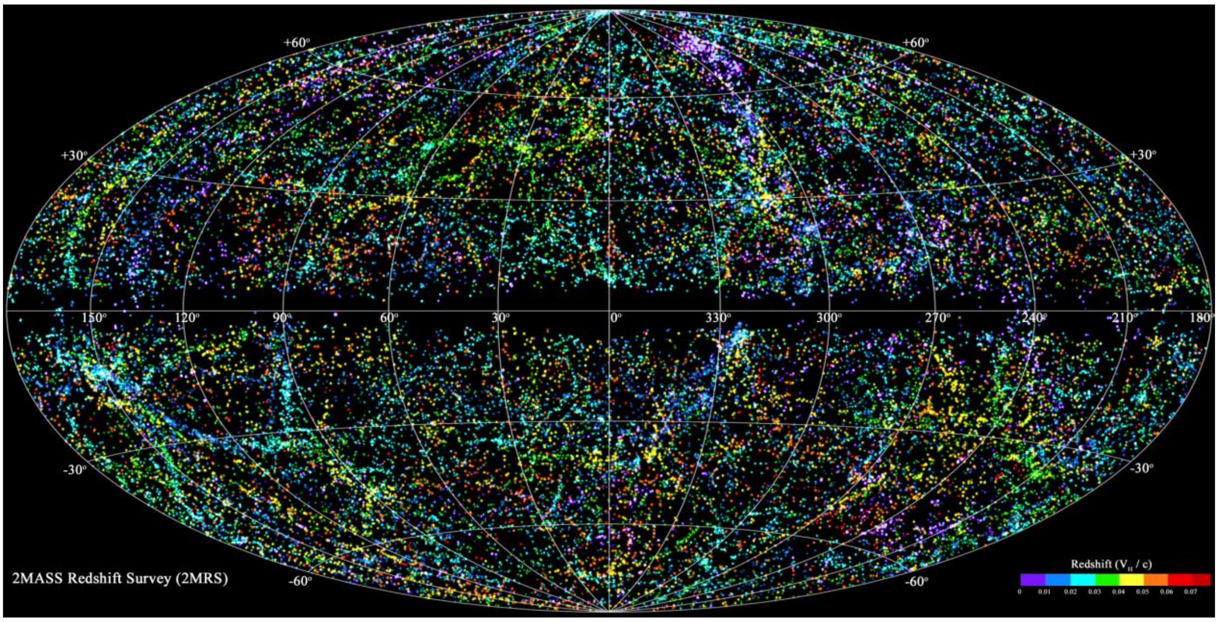

***Figure 2 :* The 2MASS Redshift Survey (2MRS) indentified 43 000 galaxies.** *The redshift z (the relativistic redshift which measures the distance of the galaxy) increases from blue to red; the most distant galaxies here are 380 millions light years from Earth (z < 0,09) (image Harward Smithsonian Center for Astrophysics, credit T.H. Jarrett (IPAC/SSC)).*

- In 2001, two different teams published the complete sequence of the human genome[9] which was a significant event even at a philosophical and moral level. This sequence provided us with information on both the origin and the modes of transition of every protein found in human bodies. This complete sequence follows the publication of many works that the older biologists were able to follow closely during the last 50 years. A lot of trial and error of even the smallest importance made it possible to first of all break up the genome, then to sequence these small fragments, and then finally to fit them to each other. This is another example of an innovation which involved thousands of articles and hours of patient and often contradictory work and which often led to dead ends.

  It also entailed the participation of teams who reached and eventually published what is now a consensus and which serves as a reference to the hundreds of other sequences that followed and have dealt with most of the

9. *The sequence of the human genome* by Craig Venter [*Science* 2001, 291, 1304-1351] and *Initial sequencing and analysis of the human genome* by a whole international consortium [*Nature* 2001, 409, 860-921]

major radiations of life (Figure 3). The practical applications in medicine and agriculture are endless.

Venter JC, Adams MD, Myers EW, Li PW, Mural RJ, Sutton GG, Smith HO, Yandell M, Evans CA, Holt RA, Gocayne JD, Amanatides P, Ballew RM, Huson DH, Wortman JR, Zhang Q, Kodira CD, Zheng XH, Chen L, Skupski M, Subramanian G, Thomas PD, Zhang J, Gabor Miklos GL, Nelson C, Broder S, Clark AG, Nadeau J, McKusick VA, Zinder N, Levine AJ, Roberts RJ, Simon M, Slayman C, Hunkapiller M, Bolanos R, Delcher A, Dew I, Fasulo D, Flanigan M, Florea L, Halpern A, Hannenhalli S, Kravitz S, Levy S, Mobarry C, Reinert K, Remington K, Abu-Threideh J, Beasley E, Biddick K, Bonazzi V, Brandon R, Cargill M, Chandramouliswaran I, Charlab R, Chaturvedi K, Deng Z, Di Francesco V, Dunn P, Eilbeck K, Evangelista C, Gabrielian AE, Gan W, Ge W, Gong F, Gu Z, Guan P, Heiman TJ, Higgins ME, Ji RR, Ke Z, Ketchum KA, Lai Z, Lei Y, Li Z, Li J, Liang Y, Lin X, Lu F, Merkulov GV, Milshina N, Moore HM, Naik AK, Narayan VA, Neelam B, Nusskern D, Rusch DB, Salzberg S, Shao W, Shue B, Sun J, Wang Z, Wang A, Wang X, Wang J, Wei M, Wides R, Xiao C, Yan C, Yao A, Ye J, Zhan M, Zhang W, Zhang H, Zhao Q, Zheng L, Zhong F, Zhong W, Zhu S, Zhao S, Gilbert D, Baumhueter S, Spier G, Carter C, Cravchik A, Woodage T, Ali F, An H, Awe A, Baldwin D, Baden H, Barnstead M, Barrow I, Beeson K, Busam D, Carver A, Center A, Cheng ML, Curry L, Danaher S, Davenport L, Desilets R, Dietz S, Dodson K, Doup L, Ferriera S, Garg N, Gluecksmann A, Hart B, Haynes J, Haynes C, Heiner C, Hladun S, Hostin D, Houck J, Howland T, Ibegwam C, Johnson J, Kalush F, Kline L, Koduru S, Love A, Mann F, May D, McCawley S, McIntosh T, McMullen I, Moy M, Moy L, Murphy B, Nelson K, Pfannkoch C, Pratts E, Puri V, Qureshi H, Reardon M, Rodriguez R, Rogers YH, Romblad D, Ruhfel B, Scott R, Sitter C, Smallwood M, Stewart E, Strong R, Suh E, Thomas R, Tint NN, Tse S, Vech C, Wang G, Wetter J, Williams S, Williams M, Windsor S, Winn-Deen E, Wolfe K, Zaveri J, Zaveri K, Abril JF, Guigo R, Campbell MJ, Sjolander KV, Karlak B, Kejariwal A, Mi H, Lazareva B, Hatton T, Narechania A, Diemer K, Muruganujan A, Guo N, Sato S, Bafna V, Istrail S, Lippert R, Schwartz R, Walenz B, Yooseph S, Allen D, Basu A, Baxendale J, Blick L, Caminha M, Carnes-Stine J, Caulk P, Chiang YH, Coyne M, Dahlke C, Mays A, Dombroski M, Donnelly M, Ely D, Esparham S, Fosler C, Gire H, Glanowski S, Glasser K, Glodek A, Gorokhov M, Graham K, Gropman B, Harris M, Heil J, Henderson S, Hoover J, Jennings D, Jordan C, Jordan J, Kasha J, Kagan L, Kraft C, Levitsky A, Lewis M, Liu X, Lopez J, Ma D, Majoros W, McDaniel J, Murphy S, Newman M, Nguyen T, Nguyen N, Nodell M, Pan S, Peck J, Peterson M, Rowe W, Sanders R, Scott J, Simpson M, Smith T, Sprague A, Stockwell T, Turner R, Venter E, Wang M, Wen M, Wu D, Wu M, Xia A, Zandieh A, Zhu X
The sequence of the human genome
Science 2001, 291, 1304-51

Lander ES, Linton LM, Birren B, Nusbaum C, Zody MC, Baldwin J, Devon K, Dewar K, Doyle M, FitzHugh W, Funke R, Gage D, Harris K, Heaford A, Howland J, Kann L, Lehoczky J, LeVine R, McEwan P, McKernan K, Meldrim J, Mesirov JP, Miranda C, Morris W, Naylor J, Raymond C, Rosetti M, Santos R, Sheridan A, Sougnez C, Stange-Thomann N, Stojanovic N, Subramanian A, Wyman D, Rogers J, Sulston J, Ainscough R, Beck S, Bentley D, Burton J, Clee C, Carter N, Coulson A, Deadman R, Deloukas P, Dunham A, Dunham I, Durbin R, French L, Grafham D, Gregory S, Hubbard T, Humphray S, Hunt A, Jones M, Lloyd C, McMurray A, Matthews L, Mercer S, Milne S, Mullikin JC, Mungall A, Plumb R, Ross M, Shownkeen R, Sims S, Waterston RH, Wilson RK, Hillier LW, McPherson JD, Marra MA, Mardis ER, Fulton LA, Chinwalla AT, Pepin KH, Gish WR, Chissoe SL, Wendl MC, Delehaunty KD, Miner TL, Delehaunty A, Kramer JB, Cook LL, Fulton RS, Johnson DL, Minx PJ, Clifton SW, Hawkins T, Branscomb E, Predki P, Richardson P, Wenning S, Slezak T, Doggett N, Cheng JF, Olsen A, Lucas S, Elkin C, Uberbacher E, Frazier M, Gibbs RA, Muzny DM, Scherer SE, Bouck JB, Sodergren EJ, Worley KC, Rives CM, Gorrell JH, Metzker ML, Naylor SL, Kucherlapati RS, Nelson DL, Weinstock GM, Sakaki Y, Fujiyama A, Hattori M, Yada T, Toyoda A, Itoh T, Kawagoe C, Watanabe H, Totoki Y, Taylor T, Weissenbach J, Heilig R, Saurin W, Artiguenave F, Brottier P, Bruls T, Pelletier E, Robert C, Wincker P, Smith DR, Doucette-Stamm L, Rubenfield M, Weinstock K, Lee HM, Dubois J, Rosenthal A, Platzer M, Nyakatura G, Taudien S, Rump A, Yang H, Yu J, Wang J, Huang G, Gu J, Hood L, Rowen L, Madan A, Qin S, Davis RW, Federspiel NA, Abola AP, Proctor MJ, Myers RM, Schmutz J, Dickson M, Grimwood J, Cox DR, Olson MV, Kaul R, Raymond C, Shimizu N, Kawasaki K, Minoshima S, Evans GA, Athanasiou M, Schultz R, Roe BA, Chen F, Pan H, Ramser J, Lehrach H, Reinhardt R, McCombie WR, de la Bastide M, Dedhia N, Blocker H, Hornischer K, Nordsiek G, Agarwala R, Aravind L, Bailey JA, Bateman A, Batzoglou S, Birney E, Bork P, Brown DG, Burge CB, Cerutti L, Chen HC, Church D, Clamp M, Copley RR, Doerks T, Eddy SR, Eichler EE, Furey TS, Galagan J, Gilbert JG, Harmon C, Hayashizaki Y, Haussler D, Hermjakob H, Hokamp K, Jang W, Johnson LS, Jones TA, Kasif S, Kaspryzk A, Kennedy S, Kent WJ, Kitts P, Koonin EV, Korf I, Kulp D, Lancet D, Lowe TM, McLysaght A, Mikkelsen T, Moran JV, Mulder N, Pollara VJ, Ponting CP, Schuler G, Schultz J, Slater G, Smit AF, Stupka E, Szustakowski J, Thierry-Mieg D, Thierry-Mieg J, Wagner L, Wallis J, Wheeler R, Williams A, Wolf YI, Wolfe KH, Yang SP, Yeh RF, Collins F, Guyer MS, Peterson J, Felsenfeld A, Wetterstrand KA, Patrinos A, Morgan MJ, de Jong P, Catanese JJ, Osoegawa K, Shizuya H, Choi S, Chen YJ; International Human Genome Sequencing Consortium
Initial sequencing and analysis of the human genome
Nature, 2001, 409, 860-921

<u>Figure 3:</u> *The complete sequencing of the human genome was carried out by two different teams and published the same year. Note the number of co-authors in each team.*

- And now the final example. The aging of developed countries' populations is something new in the history of life. Epidemiological studies have shown that we all live 2-3 months longer every year. This is also the result of an extraordinary amount of work carried out my doctors, nurses and pharmacologists who have, for example, brought down infant mortality by almost 80% and reduced cardiovascular mortality by almost a half. It is also the result of an increase in standards of living, a better diet, etc....[10] This is yet another example of work that, having been carried out patiently, eventually led to a single overall result in the history of life and which has also reached consensus.

@@@@@@@

These three examples illustrate the scientific process well. Jacob sums up this process by quoting Jean Perrin:

The heart of the problem is always "to explain the complicated visible by some simple invisible".

Firstly, the scientist proposes a hypothesis:

One can watch an object for years and never produce any observation of scientific interest

Jacob said, which is reminiscent of something that Claude Bernard said. Magendie (1783-1855), Claude Bernard's mentor, made an absolute dogma from experimentation and scepticism which he then passed down to Bernard. By doing so, just like Jacob, he opposed the "vitalists" (who are now said to fall into the same category as magicians or mythomaniacs)[11] . Perfectly summing up his character, Magendie stated "*Facts come first*", to which Claude Bernard added "*but then you must ask the right question*". It is an old debate which is still ongoing in many laboratories.

Tinkering and the savage mind: F. Jacob inspired by Lévi-Strauss

François Jacob himself gives credit to Claude Levi-Strauss (1908-2009) for introducing the concept of tinkering in his book *La Pensée Sauvage* (Plon 1962)[12]. This relationship is interesting; the "father" and the "son" are both intelligent enough to allow the "son" to take some liberties with the "father's" ideas. The comparison is very interesting. There are, however, differences in the thought of Lévi-Strauss and Jacob that amount to more than just nuances and which should be highlighted. We can single out three of them: the essential meaning of taxonomy, the founding role of

10. Swynghedauw B, Besse S. Le pourquoi du vieillissement. In *Traité de cardiologie*. Société française de cardiologie (SFC.) Artigou, JY and Monsuez JJ editors. Elsevier Masson Publishers. Paris 2007 pg 1201-1203
11. Especially the great Bichat who acknowledged the existence of vital forces that are completely different to physical-chemical forces. Let's not forget that Claude Bernard was the inventor of modern physiology.
12. In this box, the fragments of text in bold italics come from *La Pensée sauvage* (Claude Lévi-Strauss) or from Jacob (BibNum text). There is no ambiguity since the speaker is mentioned.

magical thought and the very notion of tinkering. Lévi-Strauss also broaches the subject of artistic creation which he compares to scientific creation, but clearly that is a different subject altogether.

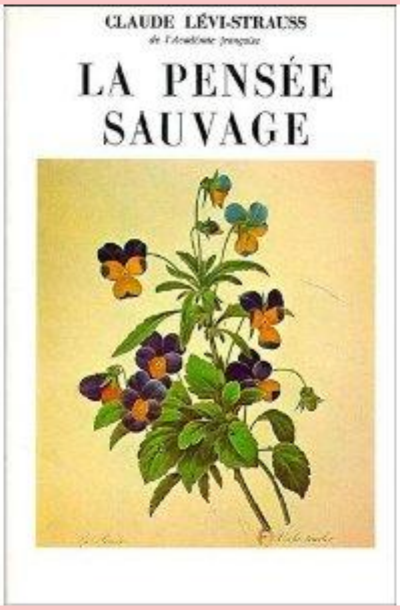

***Figure 4:* The front cover of the first edition of Lévi-Strauss's book in 1962, Plon** *(image taken from P.J. Redouté, Choix des plus belles fleurs, Paris 1827). The analogy is intentional between* la pensée sauvage *(also wild pansy in French) and the cultured mind, in the botanical sense of the term. The later editions of this book all had a wild pansy in one form or another.*

1- The essential meaning of taxonomy

The author of *Tristes tropiques* who, as we all know, was an ethnologist, always anchored his thinking on ethnographic data from surveys carried out in so-called primitive populations. He began *La pensée sauvage* by considering *the science of the concrete*. In his opinion, the best examples of this are the abstract ideas which many so-called "primitive" peoples use to characterise people and things (*the proposition: in Chinook, the bad man killed the poor child is: The nastiness of the man killed the poverty of the child…*) and also the extreme, you might even say excessive meticulousness with which these populations have themselves established their own nomenclature of plants and animals which are useful to their survival (*The Hanunóo have more than a hundred and fifty terms for the constituent parts of plants…,).* This is what Lévi-Strauss calls *Magical thought*. This meticulousness is the source of a real taxonomy which one might think is only practical in these populations, but this is not the case. The thought of Lévi-Strauss is much more subtle; such taxonomy is in fact very far from being guided by purely utilitarian considerations. In fact, the analysis carried out by Lévi-Strauss shows that this classification goes far beyond mere dietary considerations. *Species… are not known because of their usefulness. They are said to be useful or interesting because they are known first of all…Their main purpose is not of a practical nature.*

Taxonomy for Lévi-Strauss, as well as for many others, is in some ways the mother of life sciences in that it consists of organising the apparent chaos of life. This was clearly the objective of Carl von Linné's binomial nomenclature (1707-1778) [*The compleat naturalist. A life of Linnaeus*. W. Blunt] and of the monumental *Histoire naturelle* of his contemporary, Georges-Louis Buffon (1707-1780) [Buffon. G Joseph. Perrin 2011]. However, where the thoughts of Lévi-Strauss and Jacob differ is that, since Darwin, this organisation has no longer been based on simple morphological, and even less so, utilitarian considerations but rather on historical considerations. In Hennig's terms, taxonomy is in fact based on communities of origin and the existence of common ancestors. It is true, as Lévi-Strauss points out that magical thought*… is distinguished from science by an urgent demand for determinism more so than by ignorance.* Contemporary neo-Darwinian biology given us knowledge of both the limits of our ignorance and what constitutes such determinism.

2- The founding role of magical thought

A conflict exists between magic and science. For Lévi-Strauss, there is in fact *a bearing between the Neolithic Revolution and modern science … which corresponds to two distinct modes of scientific thought which are certainly not a function of the different stages of development of the human mind. Rather, they are a function of the two strategic levels where nature leaves itself open to scientific knowledge: one roughly fits into that of perception and of the imagination and the other is quite far off from it. It is as though the necessary relations which are the object of every science… could be reached by two different routes: one which is very close to sensitive intuition and another which is further away from it.*

This is a broader definition of scientific knowledge and it is hardly surprising that it was not used by Jacob. *One may disagree with the explanatory systems offered by myths or magic…. They are often charged with too much unity and coherence because of their capacity to explain anything by the same simple argument,* Jacob said. *We can go even further,* Lévi-Strauss very subtly suggests,… *and consider the rigour and the precision of magical thought… as a reflection of an unconscious apprehension of the truth of determinism - the mode of existence of scientific phenomena - so that the determinism would be generally suspected and used before being known and respected* (these words are underlined in Levi-Strauss' text). Magical rites are therefore said to be *an act of faith in a science to be born*; acts *which give the observer real "resale rights"* which have *made it possible to preserve*, until the appearance of incomparable tools of modern biology, those which brought about *discoveries authorised by nature*. In this sense, this science of the concrete is still at *the foundation of our own civilisation.*

3- The concept of tinkering for Lévi-Strauss

The tinkerer works *with the help of an extremely varied repertoire* which includes *the residue of previous constructions and destructions; just whatever the tinkerer has at his disposal.* Unlike the case of the engineer, the collection of these *elements is not defined by a project … they are all collected or conserved on the assumption that "they could still be useful"… The distinctive feature of mythical thought, like that of tinkering on a practical level, is that it develops structured sets, not directly… but by using residue…*

It is easy to see that this concept of tinkering and the use of residue and debris really appealed to Jacob because it is an area where he often applies this term. It is evolution like we show in the text (see figures 5 and 6 for example). There are many examples of speciation which has occurred thanks to broken sequences, found here and there in the midst of random genetic mutations, which are then incorporated by necessity.

@@@@@@@

However, these are two points where the thoughts of Lévi-Strauss and Jacob differ. For the former science and technology, discovery and innovation are often synonyms. The ethnologist often associates the approach of the Tewa Indians who, without knowing it, have names for all the conifers of their region even though this does not have any practical use, and that of Willy Hennig who elaborated on Darwin's thinking to establish the bases of taxonomy. Even if one does not take into account the fact that the Tewa Indians do not have any concept of "descent with modification" (which is Darwin's definition of evolution), the fact remains that the cognitive approach is of a different nature in each of the two cases. The same can be said about the classifications established by Linné which are based on morphological criteria; the bases are only observational. Establishing the hypothesis according to which there is a common ancestor to every human being and seeking confirmation of it from the structure of genes does not serve any practical interest; the important thing here is the reasoning and then the employment of methods which are capable of strengthening it.

SCIENTIFIC KNOWLEDGE – *2. DISCOVERIES, INNOVATIONS AND SCIENTIFIC RESEARCH*

When we speak about scientific research, we also speak about discovery and then innovations.

Scientific knowledge thus appears to consist of isolated islands. In the history of sciences, important advances often come from bridging the gaps.

In a famous book, Steven Johnson (see NbdP 3), by providing many examples of it, also emphasises this point and he calls these islands of knowledge “adjacent possible”. Invention and innovation (this latter term is commonly used when invention is applied technologically to a problem) arise when diversity exists and when it is moderated enough not to act as a deterrent. As a physicist, you can discover something by meeting a biologist but probably not by meeting a sociologist or psychologist because the difference is too great. This is exactly the conclusions of Rapport Hollingsworth[13] who, having attentively studied the conditions in which research was carried out in the best-performing institutes in the world (Institut Pasteur, Rockfeller, Stanford, Harvard, Yale, Cambridge, Oxford and Max Planck), raised the need for a “moderately high degree of scientific diversity”. However, the nuances are worth highlighting. Of course we need diversity, but just not too much of it. Yes, a coexistence of physicists and biologists should exist but physics and psychoanalysis probably don’t have much in common. Furthermore, the younger and complex sciences such as socio-biology probably don’t have much to offer the more ancient sciences like physics.

We will come back to this point regarding biological evolution. Again, bacteria, for example, can yield sequences of interest to vertebrates[14] but only as long as the distance is not too great. It is necessary, on the one hand, that these sequences are physically close to the potential host and that they have, on the other hand, structural elements which allow them to be incorporated into the genome of their host. The opposite process is impossible; sequences specific to a vertebrate cannot infect a bacterium because, at least historically, there is a certain hierarchy in life.

SCIENTIFIC KNOWLEDGE – *3. THE NECESSARY HIERARCHY OF OBJECTS IN SCIENCE*

Jacob gives several examples of these interdisciplinary bridges such as, for example:

> *Thermodynamics and mechanics were unified through statistical mechanics,*

---

13. J. Rogers Hollingsworth. P 02 – 003 Research organizations and major discoveries in twentieth-century science: a case study of excellence in biomedical research. See also the numerous publications by JR Hollingsworth [JR Hollingsworthet al editors.. 2002. *The Search for Excellence: Organizations, Institutions, and Major Discoveries in Biomedical Science*, New York: Cambridge University Press).

14. This is known as horizontal transmission, that is, the transmission of genes without sexual or asexual cellular division taking place, the bacterium enters a eukaryotic host cell and gives it some genetic sequences; this is how eukaryotes contain mitochondria in animals and chloroplasts in plants. Mitochondria are genetically identical to some bacteria.

and many others. The law of perfect gases is no truer in physics than in sociology but it is simply irrelevant in sociology at least in the context of this discipline. The new element of Jacob's text is this concept of hierarchy and the way he treats the classic reductionism-complexity debate.

For the pretention that every level can be completely reduced to a simpler one would result, for example, in explaining democracy in terms of the structure and properties of elementary particles; and this is clearly nonsense.

For Jacob, the solution to this endless debate must be found in the history of biology as well as in that of physics and in the constraints that this history imposes on the different strata formed this way.

> *Whatever the level, the objects analysed by natural sciences are always …systems.*

Synthetic biology made the synthesis of a molecule of deoxyribunucleic acid (DNA) possible; it has also made it possible to incorporate this artificial DNA into a cell from which its natural DNA has been extracted and to then make the cell function[15]. However, it has not made it possible to incorporate the complex system at the centre of which DNA is found (transcription, translation, not including the spatial arrangements that allow it to function) and it has not been able to regenerate a living organism, and there is nothing to say that it could do it. Even if this was possible, it would only be the copy of the pre-existing and historically predetermined complexity.

> *There is absolutely no way of estimating what was the probability for life appearing on earth. It may very well have appeared only once.*

The current state of life mainly depends on history, which has ensured the future. History, the history of France like that of life, is a science whose most important feature is its non replicable nature. The environment is also a well known constraint, but history, the history of life is a determining factor[16] even if it is often impossible to fully understand (among other reasons, for lack of many usable soft fossils, for example).

15. Craig Venter's team, the man in charge of one of the two groups to have sequenced the human genome, successfully synthesised the genome of a bacterium. Having emptied it of its original genome, they then reinserted the synthetic genome, and they managed to make it function and reproduce this bacterium with an entirely synthetic genome. This experiment is wrongly considered, because only the DNA was synthetic, the first experiment to successfully assemble synthetic life [Gibson DG et al Creation of a bacterial cell controlled by a chemically synthesized genome. Science 2010, 329, 52-56].
16. The collective work edited by J Gayon and A de Ricqlès, *Les fonctions : des organismes aux artefacts*, Presses Universitaires de France Paris 2010, is a must read to deepen this debate.

Finally,

Obviously, the two critical events of evolution – first the appearance of life and later that of thought and language – led to phenomena that previously did not exist on the earth. To describe and to interpret these phenomena, new concepts, meaningless at the previous level, are required. What can the notions of sexuality, of predator, or of pain represent in physics or chemistry?

BIOLOGICAL EVOLUTION BY MARVELLOUS TINKERING

Due to religious concerns, evolution has been considered, for a long time, as an end-result and geared towards one objective, the human being, which is considered to be perfect creation. In other words, evolution is said to be the result of engineering which takes place according to a preconceived plan for the sole purpose of creating man: the engineer either being unknown or God himself. In actual fact, evolution doesn't respond to any finalism and man is only one stage of the process and certainly not the last. However, it does have at least an apparent goal. The semantic difference is important and one can distinguish, thanks to G. Lecointre[17], three truly scientific purposes: that of teleomatic processes (example: gravity, which causes water to sink to the bottom of a tube – there is a final point but no purpose), that of teleonomic processes linked to the development of a program that "foresees" an end even though this happens unconsciously (example: the embryonic program), and that of adapted and functional systems resulting from the bringing into operation of the two previous processes, eyes are for seeing, legs are for walking.

Evolution proceeds by chance and by necessity[18]; random mutations and genetic drifts, and the necessity of natural selection as Darwin calls it. The way it works is much more like tinkering which is the term chosen and popularised by Jacob who was, as he himself admits (page 7), inspired by Claude Levi-Strauss' book, "La pensée sauvage" (see the box above).

17. Guillaume Lecointre [G. Lecointre. *Guide critique le l'évolution*. Belin. Paris 2009] gives credit to Jacques Monod and Ernst Mayr for it.
18. To plagiarise the title of the famous book by one of the other Nobel Prize winners, Jacques Monod [*Le Hasard et la nécessité. Essai sur la philosophie naturelle de la biologie moderne*. Paris. Seuil. 1970]. Details of these foundations of evolution can be found in a book that Christian Frelin and myself wrote [*Biologie de l'évolution et médecine*. Lavoisier. Paris 2011].

Evolution behaves like a tinkerer who … would slowly modify his work,… cutting here, lengthening there, seizing the opportunities to adapt it progressively to its new use.

This phrase quite adequately summarises the process and it can be illustrated by many examples. The list of examples has been extended or could have even been completed since Jacob's publication.

BIOLOGICAL EVOLUTION BY TINKERING – *1. THE EYE AND VISION; A COMPLICATED BUT EFFICIENT PUZZLE*

"The eye still makes me shudder", Darwin wrote to one of his friends. However, he added[19], "numerous gradations from a simple and imperfect eye to one complex and perfect can be shown to exist, each grade being useful to its possessor".

This phrase perfectly sums up what happened; we are, in fact, in the process of discovering all of these gradations. Conversely, the complexity of this organ has also been one of the arguments of creationists for a long time: how, say the latter, can you imagine that a structure as complex resulted from small successive steps, how can one not find there the proof of an intelligent creator[20]? The history of the eye and vision is not fully written yet but we know a lot more now in 2012[21] than what we knew when Jacob wrote his article. It is full of information on the general process of evolution and on the tinkering that presides over its origin.

19. In The Origin of Species [P.F. Collier & Son 1909] Page 190
20. There is an example of this kind of reasoning in *Le darwinisme ou la fin d'un mythe* de R. Chauvin [Rocher edition. Paris 1997].
21. See, for example, TD Lamb's journal ["Evolution of the vertebrate eye: opsins, photoreceptors, retina, and eye cup". *Nature* Reviews Neuroscience 2007, 8, 960-975].

***Figure 5:* Eyes are also an expression** *(this is a personal document belonging to the author)*

On a macroscopic level, throughout the course of evolution, there has not only been one type of eye, in fact there have been several.[22] In the most primitive animals, eyes consist of simple layers of photoreceptor cells only capable of telling night from day. Furthermore, there are eyes especially for distinguishing shape and for distinguishing colour; cat eyes, which can also see in the dark; eagle eyes which can see very far; dragonfly eyes which can even see between the fluttering of their wings; eyes which can focus on light thanks to theirs lenses and globular shape; eyes which developed from an invagination of the skin (as is the case with cuttlefish) and eyes which are partly projections of the cortex like in humans. We should also note the fact that, at least in most vertebrates, eyes are also an expression. (Figure 5).

On a molecular lever, the history of the eye is a good example of tinkering that is based on two proteins whose origins have nothing to do with vision (opsins and crystalline lenses) and also on an anatomical arrangement (Figure 6).

(i) Opsins are proteins of photoreceptor cells which capture light, trap photons and finally trigger the electric impulse which will send a message to the brain. Opsins arose by a mutation of a serpentine protein 650 million years ago. Serpentine proteins are highly polymorphic and play a very general role

22. We recommend the superb *Gallery* published in *Nature* [2008, 456, 304-309] and which shows photos of all these types of eyes.

in the transmission of signals. By chance, the mutation made this protein sensitive to light. Duplication, followed by mutations eventually gave birth to a c-opsin, stacked in the photoreceptor cells of vertebrates and to an r-opsin, stored in the membrane of the photoreceptor cells found in octopuses, for example.

(ii) Crystalline lenses are lens proteins (whose alteration lead to the formation of the cataract) which must focus light on the retina. Crystalline lenses resulted from a mutation in a *Heat-Shock Protein (HSP)*. These are themselves a category of proteins which have a completely different function altogether; they are safeguarding and stress proteins which, basically, allow the organism to maintain the functioning of every protein that makes up its body during an increase in temperature or in most states of stress.

(iii) Finally, there is a third collaborator of a different nature and that is the shape of the eyeball itself. Throughout the course of evolution, we can follow the gradual appearance of the globe. To begin with, it was only an invagination which led to the formation of a cup and which gradually took the globular shape that most vertebrates now have.

Again, man is not at the end of this process and there are, in fact, animal species whose eyes have continued to evolve, and so as to not limit themselves to vision alone, several species have eyes that have evolved even more and in other directions. Some fish, for example, have two crystalline lenses which allow them to see above and below the water surface at the same time.

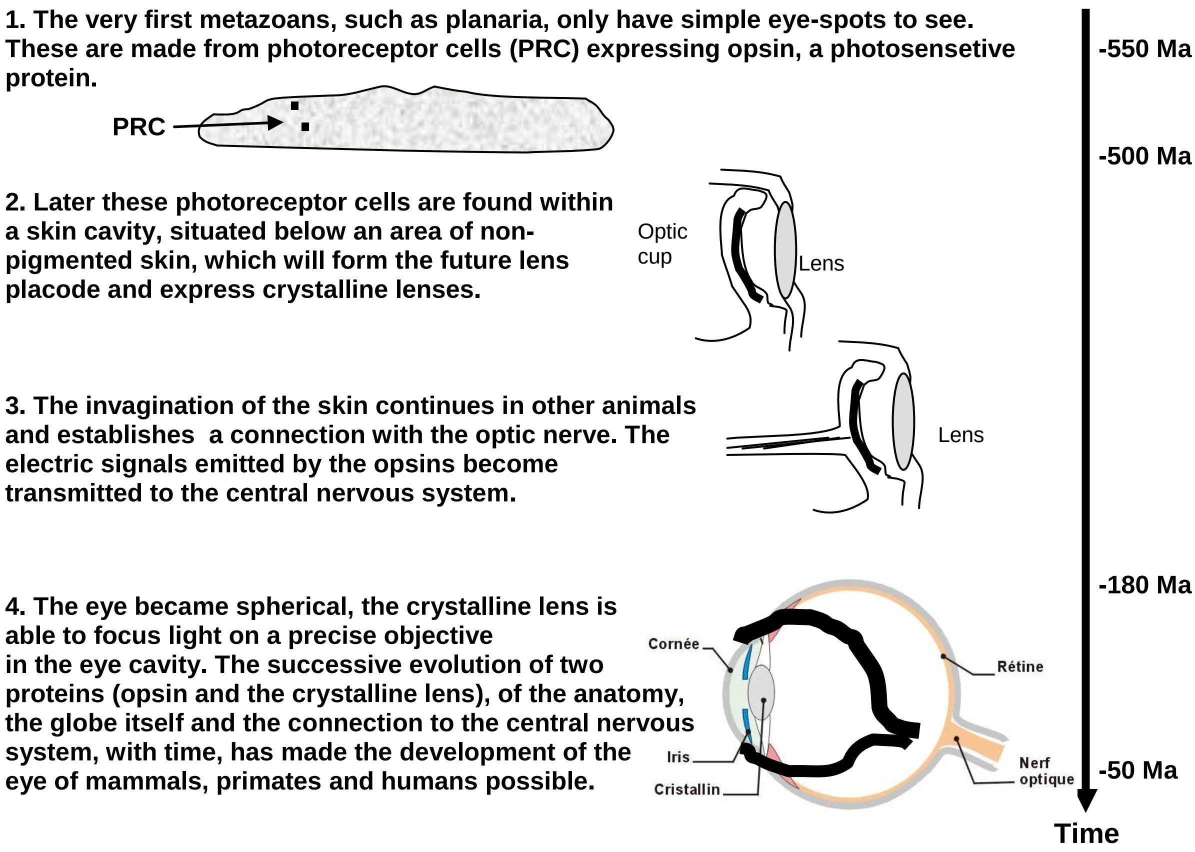

***Figure 6:* The history of vision and the origins of the eye.** *Initially, in the first chordates, vision simply sensed light, it then gradually evolved both molecularly and anatomically [redesigned and adapted from Lamb 2007 and from C. Zimmer[23]]*

This type of co-evolution is essential in the course of evolution; we will come back to it when we discuss the history of venom. The functioning of the eye as we know it requires more than just photoreceptor cells. They must be anatomically confined within a cavity, and equally they require the presence of crystalline lenses.

BIOLOGICAL EVOLUTION BY MARVELLOUS TINKERING – *2. THE SNAKE'S VENOM AND FANGS BUT IN A NON SIMULTANEOUS MANNER*

There is venom in 2000-3000 species of snakes and in 4-5 species of lizards. However, for an animal to be classed as venomous, they need to be capable of producing venom and doing so in the right place. Some animals, for

23. Lamb TD et al. "Evolution of the vertebrate eye: opsins, photoreceptors, retina and eye cup". *Nature Rev Neurosciences* 2007, 8, 960-975; Zimmer C. *Introduction à la biologie de l'évolution*. French Translation by Bernard Swynghedauw, De Boeck 2012 edition.

example, uselessly produced their venom in the pancreas for a long time. It is down to chance that venomous snakes can produce venom in their jaw and it also occurred by chance that they can quickly inject poison. Moreover, chance alone determined the date on which one or other of these compounds appeared. We know that venom appeared long before snakes did in the form that we now know them. This co-evolution has lasted millions of years and we now have the proof that one or another of these elements appeared in the right place and in the right animal (Figure 7).

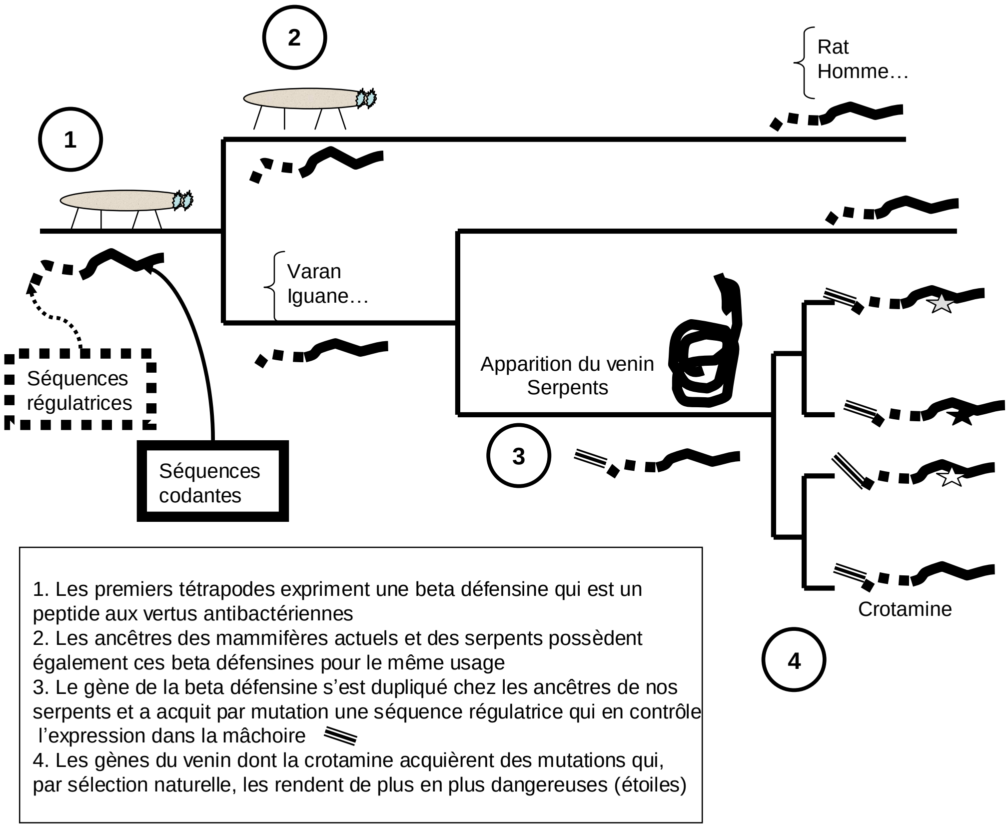

***Figure 7:* The venom gene and how crotamine was sequenced.** *The elements of this sequence were found in the very first tetrapods in the gene encoding beta-defensins which are antibacterial agents. These still exist in many mammals (and in man). Some mutations then modified these defensins as well as the system which allows the jaws, instead of the pancreas, to produce successive duplications which eventually generated the venom itself - crotamine [Redesigned and adapted from Fry 2006 and from Zimmer 2012][24]*

Crotamine, one of the best known venoms, is a myotoxin which destroys the muscle cells if injected. Its structure and the structure of the gene that encodes

24. Fry BG and al. "Early evolution of the venom system in lizards and snakes", *Nature* 2006, 439, 584-588. Zimmer see note 22.

it are both very close to that of another category of proteins – defensins. These belong to a large family of small peptides which have both direct antimicrobial properties and multiple immune activities. There are defensins in almost every vertebrate, including snakes, and they serve as antibacterial agents. The normal process of mere random mutations has caused some snakes to duplicate the defensin gene. The gene resulting from this duplication eventually mutated itself to form crotamine which became a myotoxin. At the same time, the protein, instead of being produced in the pancreas, is synthesised in the animal's jaw. The surprising thing is that we now have the proof that snakes' venom appeared in the common ancestor to snakes and lizards, that is to say 200 million years before snakes appeared themselves and before even some types of lizards lost their legs.

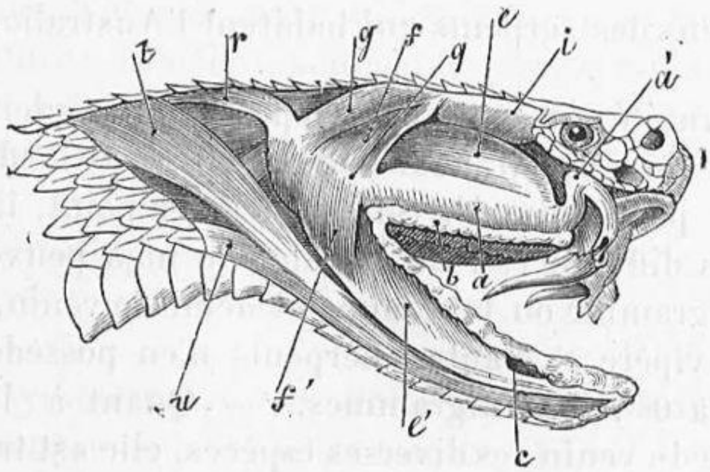

Fig. 64. — Appareil venimeux du crotale.

a, glande venimeuse ; *a'*, son canal excréteur ; *b*, glande sus-maxillaire ; *e*, glande sous-maxillaire ; *c*, *c'* temporal antérieur ; *f*, *f'*, temporal postérieur ; *g*, digastrique ; *i*, temporal moyen ; *q*, ligament articulo-maxillaire ; *r*, muscle cervico-angulaire ; *t*. vertébro-mandibulaire ; *n*, cœlo-mandibulaire.

***Figure 8 :* The venomous device of the rattlesnake** *(The rattlesnake is "serpent crotale" in French and is where crotamine takes its name from). Dr Ch. Vibert,* Précis de Toxicologie clinique & médico-légale*, 2nd edition, Baillière & fils, 1907*

INTERLUDE – THE MOLECULAR SOLUTION TO THE TWO CLASSICS OF EVOLUTIONARY BIOLOGY: UNEXPECTED DETERMINING FACTORS

Two distinguished observations have played a crucial role in the history of evolutionary biology and figure in every academic book on the subject. The first are those made by Darwin on the finches on the Galápagos Islands during his trip around the world on the Beagle. The second are those made by Gregor Mendel on garden pea plants which provide a starting point for the science of heredity and which are also crucial to understanding evolution.

Darwin noticed that each island had its own species of finches and that these differed in the size and the shape of their beak, both of which depended on the type of food available. Finches with a short thick beak lived on islands rich in hard seeds that are difficult to crunch but finches which had, on the contrary, a sharp beak only ate small worms while others with a long sharp beak could pierce the flesh of cactus plants. 14 species of finches, all with a different beak adapted to their type of nutrition, have existed on these islands for three million years.

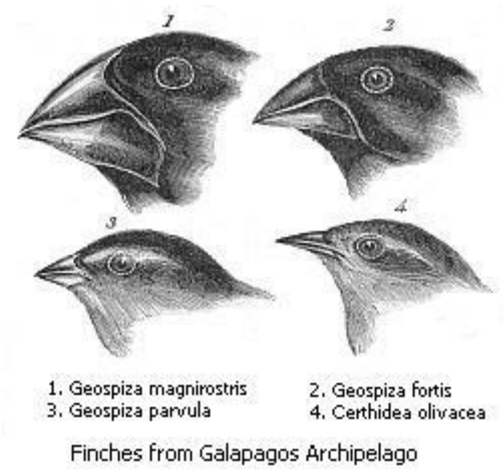

***Figure 9:* Darwin's finches.** *Charles Darwin, during his famous trip on the Beagle, made a list of several dozens of species of finches. As he always did, he measured their morphological features meticulously and he noticed that the size and shape of their beaks were adapted to their diets. Birds with a short thick beak lived on islands where a diet rich in hard seeds predominated (achenes). However, those with a long thin beak, on the contrary, fed on cactus pulp; the length and fineness of their beaks allowed them to extract this pulp.*

Many years later, in 2008, Peter and Rosemary Grant went to the Gálpagos Islands and took this work up again in order to clarify Darwin's data and to find out about molecular origins (Figure 9). Their work[25] was carried out meticulously and is a perfect example of what Jacob claimed. On Daphné Major Island, finches with fat beaks of a depth of 11 mm could crack the seeds of a plant called *Tribulus cistoides* in 10 secondes while finches with beaks of 10.5 mm needed 15 seconds. The rest of their meticulous work was in keeping with this example. However, Darwin was not outdone in terms of meticulousness and Jacob's words become clearer:

> *(Science) operates by detailed experimentation with nature and thus appears less ambitious, at least at first glance. It does not aim at reaching at once a complete and definitive explanation of the whole universe, its beginnings, and its present form. Instead, it looks for partial and provisional answers about those phenomena that can be isolated and well defined.*

Moreover, the Grants established bridges between *isolated islands of knowledge* and discovered that two proteins, and only two proteins, were involved in the process of beak formation. However, they also discovered that these proteins initially had a different function altogether. The length of the beaks depended on calmodulin which is a protein activated by calcium and plays various roles as a cofactor. Their depth depended on another protein, Bone Morphogenetic Protein 4 (BMP4) which regulates, among other things, osteogenesis- that is, bone formation). Darwin's distinguished observation was then, when all is said and done, just a small matter of tinkering.

@@@@@@@

Another classic of the discipline is the experiment on garden peas which was undertaken and immortalised by Gregor Mendel. The cross-breeding carried out by the famous monk in his garden revealed the nature of inheritance. Mendel used a botanic tool, his garden peas, to discover the laws of inheritance. This is yet another example of a patient, meticulous and seemingly modest task which led to a great discovery- the laws of inheritance, also known as Mendel's laws (Figure 8). Mendel had identified species of peas characterised by their colour, size and appearance (27 varieties in total) and chose to undertake the patient task of crossing them with each other. One of these varieties was characterised by its wrinkled appearance which contrasted with the smooth roundness of the others. The hybridisation of these two varieties resulted in 75% smooth peas

---

25. Grant PR and BR. *How and why species multiply. The radiation of Darwin's finches.* Princeton University Press, NJ publishers, 2008.

(the smooth trait being classed as dominant) and 25% wrinkled (the wrinkled trait being classed as recessive).

<u>Figure 10 :</u> Gregor Mendel (1822-1884), the founder of the laws of inheritance and the monastery garden of Brno (the capital of Moravia). *Mendel grew his peas at this monastery where he spent much of his life as from 1843 onwards.*

At that time, Mendel did not know about the very concept of genes and it was not until 100 years later that the molecular substrate of these experiments was discovered. The smooth or wrinkled trait is in fact due to the presence of a gene encoding a protein that is capable of destroying sugars, Starch-Branching Enzyme 1, SBE1. There are two different copies of the gene of this enzyme; the *R form,* which is active and the *r* form which is not. The peas that only have the *r* copy do not destroy the sugar that they contain and, as the pea grows, the sugar level increases which then draws water into the pea. However, the pea becomes wrinkled when it starts to dry. This is a second good example of a meticulous task leading to a discovery which has made an enormous impact.

BIOLOGICAL EVOLUTION BY MARVELLOUS TINKERING – *3. THE HUMAN BRAIN*

Jacob's text ends by providing basic information on the evolution of the brain. Just like the rest of our body, our brain is also the product of natural selection - that is of:

Differential reproductions accumulated over millions of years under the pressure of various environmental conditions… The human brain was formed by superposition of new structures on old ones.

What we are most proud of does not comply with anything else but the common rule. We can find traces of our neurons in the form of neuronal proteins such as reelin, or in the form of some ion channels in organisms as primitive or as early as choanoflagellates - unicellular organisms. There are also neuronal traces in the globular cells of sponges. The history of behaviour genes is also in the process of being written and sometimes evidences surprising mechanisms. However, most importantly, we can now follow the evolution and adaptation of the brain over time. Biology's first law is then, in the absence of selective pressure, the tendency of evolutionary systems towards diversity and complexity[26].

■

(March 2012)

(translated in English by Lauren Gemmell, published September 2013)

26. To use the title of the book by Daniel McShea and Robert Brandon (*Biology's first law*. University of Chicago Press, Chicago 2010).