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N° 7 Illustration et discours scientifiques. Une perspective historique

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Visual Representations and Perceptions of Lipoproteins and Atherosclerosis

In 1910 cholesterol was declared to be therapeutic; it was a time when clinical concerns were mostly directed towards infectious diseases. Beginning with the observation that infected patients were hypocholesterolemic and that the return of cholesterol to normal levels marked recovery, cholesterol liqueurs were proposed as tonics: cholesterol came to be considered as a sign of health. This is in contrast with the announcement of a wonder drug that "zaps" cholesterol in an advertisement that followed the commercialization of the first statin, lovastatin, by Merck, in the U.S.A.—the first drug that effectively lowered cholesterol (1987). Thus, cholesterol appears to be a Janus-faced molecule, to which is attributed either a harmful role or a beneficial function. And, to a certain extent, we are seeing the continuation of this duality in the current contrast between "good" and "bad" cholesterol.

Following the trajectory of the study of cholesterol across the 20th century in order to interpret the content of scientific images and their informational function, I will use images that describe, explain, classify, analyze or conceptualize, as defined by Harry Robin[1]. As visual representations add an element of persuasion to oral or written communication, they can, therefore, carry representations of distant phenomena to a single site where they can be manipulated, compared and combined in a process of dynamic hybridization and appropriation. This means that the concept of the geography of scientific knowledge put forward by David N. Livingstone[2] also encompasses visual knowledge, thus contributing to the making and reformulating of scientific knowledge, as will be demonstrated using some of the visual representations of lipoproteins. Researchers, besides conveying information through scientific images, are also concerned with them being as clear, unambiguous, simple, graphically elegant and useful as possible, a concern not divorced from aesthetics.

Coronary Heart Disease—A Public Health Problem

By the beginning of the 20th century in the U.S.A., statistics indicated an increase in coronary heart disease (CHD), but at the time the disease was considered a consequence of aging. However, the disease was also common in Russia, and there an investigator found a relationship between cholesterol and death by occlusion of the coronary arteries in rabbits fed on cholesterol.

John Gofman (1918-2007), whose parents had come to the U.S.A. from Russia, became interested in CHD. At Berkeley, using an analytical ultracentrifuge, he elucidated the movement of lipids in circulation– lipoproteins– reporting, in 1949, that Low Density Lipoproteins (LDL) increase in patients who suffer a myocardial infarction. **Figure 1** shows John Gofman next to an iconic apparatus, the analytical ultracentrifuge. The use of

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[1] Harry Robin, *The Scientific Image: From Cave to Computer*, New York, W. H. Freeman and Company, 1993, p. 9.

[2] Livingstone, D. N., *Putting Science in Its Place: Geographies of Scientific Knowledge*, Chicago, The University Press of Chicago, 2003, pp. 11-16.

the ultracentrifuge required complex calculations, which were carried out by Frank Lindgren (1924-2007), Gofman's Ph.D. student (**fig. 2**).

Figure 3 gives us the first direct look at lipoprotein particles–visual information that adds to the quantitative work. It has a descriptive function in which the image represents the way lipoproteins circulate in the blood. Lipoproteins were in this case turned into a visible image using a specific technique, electron microscopy, in order to enhance our perception abilities. This technique was developed by Thomas Hayes (b.1927), as he explains in his oral history[3]. The next illustration (**fig. 4**) is from a publication from Donner Lab. It portrays the results obtained with the ultracentrifuge. It shows the inverted peaks of the separated lipoproteins–precisely because these macromolecules float, the protein's sediment creates a peak above the baseline. We have the relative dimensions of lipoproteins determined using electron microscopy by Thomas Hayes and the concentrations of the different classes of lipoproteins requiring complex calculations, which were carried out by Lindgren. The illustration contributes to the creation of new knowledge, helping the viewer to comprehend complex information, even if its intention and function can only be fully understood by reading the text with which it is associated.

It becomes clear that science is a collaborative effort, unlike art, which tends to be autonomous. By interpreting the picture, the viewer transforms the static image into an active intellectual experience; in this case it may generate an aesthetic response, or at least curiosity. Gofman *et al.* brought their research to the attention of the public in *The Magnet*, the Lab's monthly house organ, 1959/60 (**fig. 5**). This is an image of a normal electrocardiogram. It is part of the formal mechanisms used to facilitate transfer of meaning among objects, humans and qualities in the image. The transfer is of what is known about

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[3] Hayes, T. L, *Lipoprotein Research and Electron Microscopy at Donner Laboratory*, an oral history conducted by Sally Smith Hughes, Regional Oral History Office / History of Science and Technology program, Bancroft Library, UCB, Berkeley, 2002, p. 10.

heart disease to the surrounding community, in this case people associated with the University of California-Berkeley (UCB).

National Institutes of Health and Donald Fredrikson

In **figure 6** we have Donald Fredrikson (1924-2002) at the National Institutes of Health (NIH), Bethesda, Maryland, next to another iconic apparatus, the aminoacid analyser, in 1969, when researchers started becoming curious about the protein faction of lipoproteins. The National Heart Institute was created in 1948, promoting the recruitment of young scientists as directors of research laboratories, as well as young physicians who had completed their specialty in internal medicine, which was necessary given the opening in 1953 of the new clinical center – the first hospital on the NIH campus. Among the young doctors who joined the NIH in 1953 was Donald Fredrickson.

Images that suggest a proposition tend to be more fruitful for later researchers. That is what we can observe in the next illustration, drawn by Fredrickson (**fig. 7**). In 1958 there was not a scale for the lipoprotein particles, so in 2008 there was a dynamic hybridization with the introduction of the diameter on the x axis; this sparked a reinterpretation, giving new meaning to the image. And this picture has a second function, a significant pedagogical content.

The act of classification is an attempt to discover some semblance of order in Nature. Knowledge must be codified and stored so that succeeding observations may be compared and differences, however subtle, can be investigated and clarified (**fig. 8**). By bringing order and clarity to an illustration, specifics may suggest generalizations. Scientists must revise their explanations when they uncover a previously hidden aspect of a phenomenon. That is how this classification was later modified.

Cholesterol, being insoluble in aqueous solution, is transported in plasma in association with specialized proteins – apolipoproteins (**fig. 9**). We have descriptive names for biochemical compounds; this figure enhances "nonverbal reasoning ability." Indeed, the structure of a lipoprotein is not easily reduced to words.

Apolipoproteins and the Lipoprotein Concept of Petar Alaupovic

There are laboratories that force a change in itinerary which others follow, recruiting more participants from faraway places. Petar Alaupovic's laboratory was one such example (**fig. 10**). In the publication of the David Rubinstein Memorial Lecture[4], Alaupovic (1923-2014), when transcribing the words of the poem "The Road Not Taken," by Robert Frost, expressed his own journey:

> I shall be telling this with a sigh
> Somewhere ages and ages hence:
> Two roads diverged in a wood, and I—
> I took the one less traveled by,
> And that has made all the difference.

The study of lipoprotein families and determination of apolipoproteins are inextricably linked to Alaupovic (**fig. 11**). Scientists have always found ways of making people believe that phenomena illustrate themselves. Alaupovic introduced a new technique to isolate lipoproteins according to their composition of apolipoproteins, based on immunoaffinity cromatography. Such thought experiments may be generated by dissatisfaction with previously expressed explanations; by new or faintly glimpsed observations; or by a heightened state of awareness of subtle, intangible discontinuities. In the sciences, the memory of observed phenomena, illustrations, and quantitative relationships are subject to mental scanning and meditation that may produce new insights. It seems we cannot think about an observation or experience in the objective world without resorting to mental imagery.

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[4] Alaupovic P., David Rubinstein Memorial Lecture: "The Biochemical and Clinical Significance of the Interrelationship between Very Low Density and High Density Lipoproteins," *Canadian Journal of Biochemistry*, 59, 1981, pp. 565-579.

The Atherosclerotic Process

The observation of a repeated pattern provokes the scientist to seek the cause of the phenomenon, and that is how scientists were able to understand the atherosclerotic process. A histological section is also among the conventionally accepted resources that can be interposed between the phenomenon and the investigator to capture the event for analytical study, another way of "making phenomena illustrate themselves," (**fig. 12**). The fundamental lesion of atherosclerosis is the fibro-fatty plaque. Atherosclerosis develops over several years and may be asymptomatic. It tends to affect the inner walls of large and medium-sized arteries, resulting in narrowing of the vessel. Symptomatic atherosclerosis may occur in minutes and the clinical consequences can include coronary artery disease, cerebrovascular disease or peripheral vascular disease (claudication, gangrene). The atherosclerotic lesion is essentially an injury of the arterial wall caused by the lipids in the blood stream invading it. The most relevant fact that supports the association between elevated levels of cholesterol and the process of atherogenesis and of coronary heart disease was described in 1938 in relation to homozygous familial hypercholesterolemia (FH), a hereditary condition characterized by extremely high cholesterol[5].

The Search for the Fundamental Deficiency in Familial Hypercholesterolemia

Two researchers, Michael Brown (b.1941) and Joseph Goldstein (b.1940), first met during their internship at Massachusetts General Hospital in Boston (1966–1968) and share a great interest in the molecular basis of the disease, i.e. in the process of molecularization. Both later went on to the NIH. Brown and Goldstein used to discuss patients with abnormalities of lipid

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[5] Müller, C., "Xanthomata, Hypercholesterolemia, Angina Pectoris," *Acta Medica Scandinavica*, 89, suppl., 1938, pp. 75-84.

metabolism, in particular patients' homozygous for familial hypercholesterolemia. It was at the NIH that Goldstein, originally from Dallas, asked Brown to go to the University of Texas Health Science Center in Dallas to work on the genetic regulation of cholesterol metabolism. They hoped to clarify the biochemical mechanism by which a single gene increases cholesterol levels in this rare patient group of hypercholesterolaemic homozygotes on a molecular level (**fig. 13**).

The team had an experimental system which they believed to be a useful approach in the search for the fundamental deficiency, apparently genetically defined in FH, and causing a defect in the regulation of cholesterol synthesis at the level of HMG-CoA reductase. This suggested the hypothesis of a receptor on the membrane surface binding to an LDL receptor. As a result of this binding, a second messenger would be generated suppressing the activity of the reductase.

Experimentation reflects the scientist's desire to observe or experience the operation of cause and effect in order to verify or reject a hypothesis. Brown and Goldstein used the technique of growing cells in culture, which was relatively new in 1972. The notion that cultured cells might allow pinpointing of metabolic errors was still newer. Thus they introduced cell biology into the study of lipoproteins, again as a means of "making phenomena illustrate themselves." An illustration was worked up to make its visualization and interpretation as direct as possible (**fig. 14**).

Akira Endo and the Discovery of Statins

Knowledgeable about cholesterol synthesis and also aware that the limiting step of the synthesis is the one in which HMG-CoA reductase intervenes, Akira Endo (b.1933) thought that an inhibitor of this enzyme would be an effective agent in reducing cholesterol levels. And because the company where he was in 1971 was carrying out studies on fungi, he speculated that just as some species inhibit bacterial growth, others could inhibit the synthesis of cholesterol.

Over a two-year period, Endo's team tested more than 6,000 fungi for their ability to block cholesterol synthesis. In 1973 they finally found one strain of fungus that produced an active compound. The fungus belonged to the same genus that produced penicillin, the reason some people call the statins "penicillin for the heart." **Figure 15** shows how Brown and Goldstein's work strongly supported Endo's studies and his idea of developing HMG-CoA reductase inhibitors.

It is this use of Nature that sets their work apart, and when communication of an understanding of Nature through images allows the scientist to say, "This is how it works," the picture, to a certain extent, becomes the theory; subsequently, research and experimental practice will be stimulated. According to Chadarevian and Kamminga[6], it is rare to have a convergence of etiology, diagnosis and therapy; i.e., knowing the mechanisms of disease and the diagnostic at a molecular level does not imply that a molecular cure is available. In the case of hypercholesterolemia and of statins, the mechanism of the action of the therapeutic molecule is not the only known factor, and statins have few side effects, being considered safer than aspirin[7].

Scientists' images always aim to give what they consider to be the most rational version of phenomena. However, how specific traits should be visualized and how to pick the perfect image depend to a large degree upon pragmatic categories and local factors within individual laboratories and research groups, as well as on editorial decisions and promotional value. Experimental scientists work with a combination of action, instruments,

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[6] Chadarevian, S., Kamminga, H., Introduction, *Molecularizing Biology and Medicine: New Practices and Alliances, 1910s-1970s*, eds. Chadarevian, S. and Kamminga, H., Amsterdam, Harwood Academic Publishers, 1998, pp.1-16.

[7] Steinberg, D., *The Cholesterol Wars: The Skeptics vs. The Preponderance of Evidence*, Amsterdam, Elsevier, 2007, p. 199.

objects and procedures as well as words, that is, with a significant non-verbal component of communication.

Visualization is thus an integral part of the understanding and evolution of new scientific concepts and boundaries. The images made for pragmatic and heuristic purposes in the laboratory evolve into those that are chosen for posters and lecture presentations, images accompanying article submissions, and finally those that will be selected for public presentation and communication. We conclude, simply, with a work of art by Alexandra Alaupovic entitled "A Tribute to Lipoprotein Particles" (**fig. 16**).