A Hempelian Explanatory Shift in Neuropathology: A Study in the History and Logic of Medicine*

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Abstract. Mechanistic analysis of infarction along the boundary zones between the major arterial territories (watersheds) in the brain is herein described as an example of a scientific explanatory shift. The two explanations for the pathogenesis of watershed infarction were both logically deduced from radically different empirical laws of fluid mechanics. The first explanation became the orthodox or received view only until incompleteness necessitated the development of an alternative and autonomous explanation which accounted for the empirical phenomenon that the orthodox explanation could not logically infer. Since this explanatory shift emerged to maintain completeness, and used empirical laws (Bernoulli's law and the Fahraeus-Lindqvist effect) as antecedents for the logical deduction of consequents which were empirically testable by experiment, it is suggested that the explanatory shift was of the Hempelian-type.

Résumé. L'analyse mécaniste de l'infarctus qui se produit le long des zones fontières entre les territoires arteriels les plus importants dans le cerveau est décrite ici comme un exemple de changement dans le mode d'explication scientifique. Les deux explications pour la pathogenèse de ce type d'infarctus étaient toutes deux logiquement déduites de lois empiriques sur les fluides mécaniques radicalement différentes. La première explication demeura la conceptions orthodoxe ou acceptée jusqu'à ce que son incomplétude ait nécessité le développement d'une explication alternative et autonome qui permettait de rendre compte du phénomène empirique que l'explication orthodoxe ne pouvait pas impliquer logiquement. Comme ce changement dans le mode d'explication a été produit pour maintenir la complétude et qu'il utilisait des lois empiriques (La loi de Bernoulli et l'effet de Fahraeus-Lindqvist) comme antécédents pour la déduction logique de conséquences qui étaient empiriquement vérifiables par l'expérimentation, il est suggéré que ce changement a été du type hempélien.

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HEMPELIAN EXPLANATION

Empirical science is the process where observable data of a specific research problem is collected and correlated with other empirical findings in the same research domain. Once the correlations have been made a general proposition is formulated to describe the observed regularity. In contrast, there are empirical laws which are not specifically limited to the narrow domain of one empirical research problem but are determined by a similar inductive process. Empirical laws are usually stated as quantitative algebraic relations (e.g., Boyle's law) but in many qualitative sciences may take the form of logical propositions.

Hempel has shown that explanation of an observed empirical phenomenon or correlation is a logical process where the logical conclusion is the empirical phenomenon to be explained and the premise propositions are empirical statements including empirical laws which have truth value. The deduction of the logical conclusion from the premise statements by logical necessity ("the Transmission principle") is, therefore, scientific explanation. It follows directly, that corroboration of the explanation is one of the roles of experimentation since if the explanation is logically valid the conclusion should be observable or measurable in the empirical world. In this way, a consequent of scientific explanation can be defined as an hypothesis which has empirically testable adequacy. One further feature of Hempelian explanation which is relevant to the analysis in this paper is senescence. The completeness of an explanation may be transient in time since new observations may emerge which are not logically deducible within the orthodox explanation. Such incompleteness is an indication for an explanatory shift in which an autonomous explanation is developed which includes premise propositions which may not have been incorporated in the orthodox explanation.

For the purposes of the present discussion, the problem of adding a pathogenetic mechanism for watershed infarction can be divided into discrete stages: (1) empirical research in which observations and correlations were listed, (2) explanation of empirical data, (3) identification of an empirical phenomenon which could not be inferred by the orthodox explanation, and (4) development of a new explanation.

THE PROBLEM OF WATERSHED INFARCTION

Watershed infarcts (or cerebral granular atrophy) are regions of cerebral ischemic necrosis that are characterized by a distinct topography determined by the anatomy of the cerebral arterial circulation. The arterial supply of the cerebrum is broadly divided into three arterial territories, each supplied by a major cerebral artery, that overlap in a boundary zone or watershed. Watershed zones have two other signifi-
cant characteristics: (1) they represent the most peripheral extensions of the arterial territories in the brain, and (2) the major arteries which supply the zones give rise to arteries which supply most of the brain's surface area, and these arteries are consistently smaller than the parent vessel which supplies arterial blood to the watersheds.

Most infarcts occur randomly in a variety of brain sites, and may be caused by occlusion of a blood vessel or by failure of blood flow for other reasons such as decreased perfusion pressure. Watershed infarcts are of particular importance because they occur in such a highly restricted and characteristic pattern. This leads to the question: By what mechanism does infarction occur preferentially in the watershed zones?

OBSERVATIONS, CORRELATIONS, AND GENERALIZATIONS

Giovanni Batista Morgagni, the eighteenth-century morbid anatomist, was probably the first to describe the essential morphologic features of watershed infarction in the earliest comprehensive work in pathology, *The Seats and Causes of Disease as Investigated by Anatomy*. Subsequently, modern pathologists such as Blackburn further documented the topographic and structural features of watershed infarction by photographing granular atrophy preferentially involving the watershed zones in brains of inmates from an insane asylum. Penteschew corroborated previous findings with the description of nine additional cases, while Lindenberg and Spatz, and independently Meyer, made further descriptions of brains and added the microscopic findings of occlusive changes in small arteries restricted to the brain. Over a 34-year period four research groups working independently confirmed earlier reports as well and noticed the association with atherosclerosis of the carotid arteries and sometimes systemic hypotension according to retrospective studies of patient records.

The long period of investigation (1750-1964) allowed for the comprehensive correlation of morphologic findings in dozens of cases of watershed infarction. The correlations were summarized by Romanul and Abramowicz in their comprehensive paper of 1964; these were made due to the high frequency of concurrence between repeatedly observed features, the most important of these being: (1) the high specificity of infarcts along the watershed zones, (2) stenosis of the carotid arteries due to atherosclerosis or in some cases systemic hypotension, and (3) occlusion of small blood vessels overlying the watershed zones.

ZULCH'S EXPLANATION

Zulch proposed that since watershed zones are in the regions of the cerebrum which have the most peripheral arterial supply, any
decrease in perfusion pressure proximal to the watershed would result in inadequate perfusion of the watershed zone. This so-called "last-ditch-effect" or "terminal-irrigation-field-effect" is a simple application of Bernoulli's relation to tapering vessels. Essentially, the carotid-cerebral arterial supply is a volumetrically closed system in which pressure at the level of the heart determines the relative distance blood will travel up the carotid arteries and their branches. Zulch argued that under normal systolic pressure (120 mm Hg) the entire cerebral arterial tree is perfused; however, a decrease in systolic pressure to some threshold value may be sufficient to impair volumetric distension of the distal parts of the system—the watershed zone. Zulch observed that the critical threshold was about 60-70 mm Hg, and that stenosis of the carotid arteries could also cause a sufficient drop in watershed perfusion.

Within two years of Zulch's theory, a clinicopathologic study reported a further series of cases of watershed infarction, all correlating with clinically proven systemic hypotension and specifically lacking occlusive changes of the overlying blood vessels often found in other cases. As well, an experimental group reproduced watershed infarction in primates by inducing hypotension both pharmacologically and by clamping the carotid arteries. Based on the explanation's simplicity and the experimental scrutiny, the first basis for watershed infarction pathogenesis was generally accepted by the late 1960s.

The major weakness in the explanation was that although it integrated many pathological features of watershed infarcts, it did not explain them all; in some cases occlusive changes of blood vessels were restricted to infarcted regions of the brain. These vascular lesions could not be definitively explained on the basis of a pressure deficit (without an ad hoc assumption) and were not a feature of the experimentally-induced watershed infarcts of the primate model. Further difficulties with Zulch's proposal arose in 1970 when Price and Harris reported cholesterol crystals occluding the small arteries overlying watershed infarcts. The cholesterol ester crystals had presumably entered the cerebral circulation by dislodging from some local arterial site proximal to the watershed and had been carried by the flow of blood to the brain. After the Price and Harris paper four additional reports also correlated watershed infarction with embolism.

THE EMBOLIC EXPLANATION

Another explanation for watershed infarction was necessary to account for the development of cerebral infarction in individuals who were normotensive, had patent carotid arteries and had occlusive changes in arteries overlying the infarcts. Although the pathological evidence suggested that the infarcts could be due to ischemia from
local occlusion of the watershed blood vessels by the propagation of dislodged particles (emboli), no one seriously considered this prior to 1982. There were three major reasons for this. First, the explanation had to account for the selective distribution of emboli to the watersheds and not elsewhere in the brain, and previous experimental work suggested that this did not occur. Secondly, Zulch’s theory had become the orthodox explanation, such that Price and Harris expressed doubts that emboli could cause watershed infarcts in their case report. Third, not only were the emboli not randomly distributed but they were limited to a specific size range averaging 200 micrometers in size. A new explanation had to explain why the preferential distribution of emboli should only occur with particles of a limited size.

In 1989, the embolic explanation of watershed infarction was proposed that could, in principle, account for all the structural findings described in those cases of watershed infarction not accounted for by Zulch’s explanation. Surprisingly, the embolic explanation could not only explain the presence of occluded small arteries, and meet the two other criteria listed above, but it also allowed a logical prediction. Unlike Zulch’s explanation the new proposed mechanism was not based on Bernoulli’s law but rather on the Fahraeus-Lindqvist effect.

The Fahraeus-Lindqvist effect (plasma skimming) states that the viscosity of a suspension of particles flowing through bifurcations will change, such that one of the branches has a suspension of particles that is less viscous than the parent trunk. When applied to suspensions of particles the Fahraeus-Lindqvist effect is explained by two fundamental properties of the flow of suspended particles in blood: (1) suspended particles are distributed along a radial concentration gradient such that a marginal layer of plasma, containing few or no particles, is found in the most peripheral streamline (streamline nearest the wall of the parent vessel), and (2) that fluid entering an asymmetrical or uneven branch of a bifurcation is derived from the peripheral streamline. Under these conditions, a fully developed radial concentration gradient of suspended particles flowing through a bifurcation will result in the concentration of particles in the segment of the main trunk after the bifurcation, since particles tend to remain in the axial stream. The embolic explanation further extended the Fahraeus-Lindqvist effect by postulating that the radial gradient in the parent vessel is mediated by the size of the suspended particle, such that large particles are more concentrated in the axial stream than smaller ones, so the concentration of large particles in an asymmetric branch will be less than the smaller ones.

Applying this to embolism in cerebral arteries, it was proposed that emboli near 200 micrometers in size were distributed along a radial concentration gradient in major cerebral arteries, so the majority of embolic particles
remain in an axial stream in parental arteries rather than diverging into asymmetrical branches which emerge from the main trunk (see figure). Accordingly, the main or parent artery had a radial concentration gradient of emboli, and the branch derives emboli-laden blood from the perimeter of the parent vessel. The resultant concentration of particles in the branch is less than the trunk after the bifurcation, and in this way emboli tend to remain in the parent vessel. Since the parental arteries are generally watershed-bound, the embolic particles would be selectively propagated to watershed zones where they lodge and cause infarction. The explanation integrates all the features that Zulch's theory failed to account for and does not rely on it in any way; it is autonomous.

Two-dimensional representation of the embolic explanation. Emboli in a critical size range are distributed along a radial concentration gradient in watershed-bound cerebral arteries. Emergent branches which supply non-watershed brain regions have smaller radii than the main artery and derive flow from the periphery of the gradient. On this basis, emboli are preferentially directed to watershed zones and cause selective infarction. Arrow indicates direction of flow.

Steegman and de la Fuente had previously perfused rabbit brains with emboli in a size range of less than 200 micrometers and found that particles did not selectively distribute to the watersheds;\(^{21}\) another experiment had to be designed to see if selective embolization occurred with particles in the 200 micrometer range. Using a human cadaveric perfusion model, when particles less than 150 micrometers in size were perfused into the brain, Pollanen and Deck found no selective distribution of particles.\(^{22}\) However, under the same conditions, when particles averaging 200 micrometers were perfused into the cadaver brains,
they found there was selective propagation to the watersheds. Since selective embolic distribution was reproduced in a human brain an additional experiment had to be designed to see if the explanation based on the size-mediated Fahraeus-Lindqvist effect could account for it.

To this end, physical models of arterial branches consisting of evenly and unevenly bifurcating cylinders were constructed and used as perfusion systems. Perfusion of the bifurcations with 200 micrometer particles showed that decreasing the size of the branch resulted in decreased concentration of particles in the branch. In contrast, as expected, particles less than 100 micrometers in size had no relative concentration shift along the bifurcation. This experimental evidence indicated that asymmetric branches arising from watershed-bound vessels could contain fewer emboli than watershed-bound arteries, due to profile of the concentration gradients in the vessel being mediated by the size of suspended particles. Other biorheologic experiments have also been reported which are consistent with the size-mediated Fahraeus-Lindqvist effect. A marginal layer of plasma containing no blood cells has been found in capillaries and arterioles and has been reproduced in vitro. In these experiments suspensions of human blood were perfused through narrow tubes (12-112 micrometers) and erythrocytes were found to be distributed across a radial gradient with the highest concentration of erythrocytes in the main inertial axis of the tube. Platelets in the blood suspensions, however, were distributed along a different gradient such that the concentration of platelets in the axial and peripheral streams differed only slightly. Since platelets are minute, relative to erythrocytes, this is analogous to the findings with macroscopic particles flowing through bifurcations. Whether or not the fluid mechanical mechanism involved in radial gradients in the 12-112 micrometers system is similar to that of cerebral arteries, which are several orders of magnitude larger, will require theoretical clarification.

LOGICAL PREDICTION FROM THE EMBOLIC EXPLANATION

The best explanations in science often predict novel empirical events by forecasting the observation of some phenomenon not previously described. The embolic mechanism for watershed infarction provides a logical prediction which can be inferred from the two necessary conditions for selective embolization—embolic laminar flow (size-mediated Fahraeus-Lindqvist effect) and asymmetric arterial branching. Any arterial system with these two characteristics will have one or more watershed zones to which laminar flowing suspended particles will be propagated. The heart, like the brain, contains an arterial supply characterized by asymmetrical branching, and has a corre-
sponding zone where distal segments of main coronary arteries converge. Based on inspection of radiographs of postmortem hearts injected with contrast medium (in the coronary arteries) this zone is found in the inferior portion of the interventricular septum.

Since the coronary arteries arise directly from the aorta upon its exit from the heart, embolic particles present in the outflow stream would enter the coronary circulation. Thus, the embolic mechanism of watershed infarction predicts that infarcts of the myocardium in the inferior portion of the interventricular septum should occur under circumstances where appropriate sizes of emboli are present in the coronary network. The most likely and common circumstance for this would be marantic (thrombotic non-bacterial) endocarditis. A comprehensive study of myocardial changes in marantic endocarditis has not yet been done to detect these undiscovered but predicted lesions.

CONCLUSION

The events leading to the development of the Zulch and embolic explanations were incremental and essentially can be described as "normal science"28 or the empirical phase of investigation.29 The explanation of Zulch gained general acceptance as an orthodox explanation within a short time since it completely explained all neuropathological features of watershed infarction up until the discovery of Price and Harris. The rise of the embolic explanation was initiated to restore explanatory completeness.

Clearly, both explanations meet the necessary criteria for Hempelian explanation. Zulch used Bernoulli's law to explain the ischemia of terminal arteries and Pollanen and Deck used the Fahraeus-Lindqvist effect to explain the directed propagation of emboli to the watersheds. These empirical laws became premise propositions in logical arguments in which valid deductions were possible (see Appendix). As well, the conclusions of both logical arguments were necessarily empirical and experiments could be designed to empirically corroborate the inferences of the explanation. In the case of Zulch's explanation, Bernoulli's law allowed the deduction of an existential statement of watershed infarcts caused by hypotension, and primate experiments were designs to see if such infarcts could be reproduced under controlled conditions. Similarly, the experimental test of the embolic explanation required reproduction of differential embolism in a human brain and proof that the size-mediated Fahraeus-Lindqvist effect could occur in physical models of cerebral arteries. It is clear that the explanatory shift (from Zulch to embolic) was the result of considering radically different laws of fluid mechanics as important variables in the pathogenesis of watershed infarction. On this basis, if a further empirical discovery is made in cases of watershed infarction, explanatory completeness may
need to be restored with the use of some different fluid law. An alternative route to explanatory completeness is the development of an \textit{a priori} general theory of cerebral infarction, which is currently under investigation.

**APPENDIX**

\textit{The Deducibility of Embolic Watershed Infarction}

A naive modal system, $DM$, is developed to formalize the explanation of embolic watershed infarction. The sentential connectives and modal operators are used in the usual way; there are six replacement identities (R1-R6) and two inference rules (R7 and R8).

R1: $\neg(\phi \lor \varphi) \rightarrow \neg \phi \land \neg \varphi$ (and dual)
R2: $\Box \phi \rightarrow \Box \neg \phi$
$\neg \Box \phi \rightarrow \Diamond \neg \phi$
$\Diamond \phi \rightarrow \Box \neg \phi$
$\neg \Diamond \phi \rightarrow \Box \neg \phi$
R3: $\phi \Rightarrow \varphi \rightarrow \Diamond \phi \lor \Box \varphi$
R4: $\Diamond (\varphi \land \gamma) \rightarrow (\Diamond \varphi \lor \Box \gamma)$ (and dual)
R5: $\Box (\Diamond \phi) \rightarrow \Box \phi \lor \Box \varphi$ ($\Box$ can be replaced by any modal operator and $\lor$ can be replaced by any sentential connective.)
R6: $\Box \phi \lor \Box \varphi \rightarrow (\Box (\Diamond \phi) \lor (\Box (\Diamond \varphi))$
R7: If $\phi$ and $\varphi$ are theorems then $\phi \land \varphi$ is a theorem and if $\phi \land \varphi$ is a theorem so are $\phi$ and $\varphi$.

In R1, R3, R4, R7, and R8, $\phi$, $\varphi$, and $\gamma$ are read as sentence letters with a modal operator and in all other cases $\phi$, $\varphi$, and $\gamma$ are sentence letters. Rule 6 is T8 of the well-known modal system T. Henceforth, $\phi$, $\varphi$, and $\gamma$ are sentence letters and may represent $E$ (emboli), $W$ (watersheds), $C$ (hypoperfusion), $O$ (occlusions), and $I$ (infarcts). The axioms of $DM$ follow naturally from the text; these are:

A1: $\Box (E \Rightarrow W)$
A2: $\Box (O \lor C) \Rightarrow \Box I$
A3: $\Diamond (E \land O)$

Now the possibility of embolic watershed infarction, $\Diamond (E \lor W \lor I)$ can be deduced.

T1: $\Box E \Rightarrow \Box W$  \hspace{1cm} A1, R5
T2: $\Box (E \Rightarrow \Box W) \Rightarrow (\Box E \Rightarrow \Box W)$  \hspace{1cm} T1, R6
T3: $\Diamond E \Rightarrow \Box W$  \hspace{1cm} T2, T1, R7
T4: $\Box (O \lor C) \Rightarrow \Box I$  \hspace{1cm} A2, R5
T5: $\Box (\Box (O \lor C) \Rightarrow \Box I) \Rightarrow (\Box (O \lor C) \Rightarrow \Box I)$  \hspace{1cm} T4, R6
Although this is obviously a weak modal system, if it does truly represent the empirically corroborated embolic explanation it should be contradiction-free (negation consistent). This will now be shown.

**Metatheorem:** DM is consistent.

**Proof:** By repeatedly applying the inference rules it is easily shown that all theorems with one sentence letter are in the form $\Diamond \phi$ (case 1). As well, all other theorems can be reduced to one of four general formulae using only two sentential connectives: $\Box \phi \Rightarrow \Box \psi$ (case 2), $\Diamond \phi \Rightarrow \Box \psi$ (case 3), $(\Box \phi \lor \Box \psi) \Rightarrow \Box \gamma$ and $(\Diamond \phi \lor \Box \psi) \Rightarrow \Box \gamma$. If DM is negation consistent then the negations of these general formulae must not be reducible to any other of the general formulae. For case 1 we have already established that all theorems with one sentence letter must be in the form $\Diamond \phi$ so the negation is not a theorem. In case 2, the negation is $\Box \phi \land \Box \psi$ where each of the conjuncts are not theorems, as stated in case 1. In case 3, the negation gives $\Diamond \phi \land \Box \psi$ but $\Box \phi \land \Box \psi$ is not a theorem so the conjunct is not a theorem. In case 4, the negation reduces to $(\Box \phi \lor \Box \psi) \Rightarrow \Box \gamma$ where $\Box \phi \land \Box \psi$ has already been rejected in case 2. Finally, in case 5, the negation gives $(\Diamond \phi \lor \Box \psi) \Rightarrow \Box \gamma$ where $\Box \phi \land \Box \psi$ has already been rejected in case 3. This ends the proof for consistency and validates the claim for DM’s representability for embolic watershed infarction.

**NOTES**

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7. Romanul and Abramowicz, “Changes in Brain and Pial Vessels.”
9. Romanul and Abramowicz, “Changes in Brain and Pial Vessels.”
16. Price and Harris, “Cholesterol Embolization in Cerebral Arteries.”
17. Price and Harris, “Cholesterol Embolization in Cerebral Arteries,” and Pollanen and Deck, “Directed Embolization is an Alternate Cause.”
18. Pollanen and Deck, “Directed Embolization is an Alternate Cause.”
21. Steegman and de la Fuente, “Experimental Cerebral Embolism. II.”
23 Pollanen and Deck, "The Mechanism for Embolic Watershed Infarction," Fig. 1b.
24 Pollanen and Deck, "The Mechanism for Embolic Watershed Infarction," Fig. 3.
25 Pollanen and Deck, "The Mechanism for Embolic Watershed Infarction," Fig. 2.
29 Robinson, Renascent Rationalism.