

neuron. Thus, the sensory neuron along the CS pathway will be better able to activate the motor neuron and produce the CR.

Another example of associative modifications in an individual neuron can be found in the marine mollusc *Hermisenda* (j). Light is paired with 5-HT application in an analogue of classical conditioning. As with classical conditioning of the withdrawal reflex in *Aplysia*, 5-HT can also act to mediate reinforcement in *Hermisenda*. The conditioning results in both an increase in the excitability of a single cell and an enhancement in the strength of a specific type of synapse.

3. Conclusion

With classical conditioning of the *Aplysia* withdrawal reflex, the paired CS and US form an association by converging on a second messenger cascade within a single cell. This convergence results in the enhancement of a specific synapse. With operant conditioning of *Aplysia* feeding behavior, the association is made through contingent reinforcement. Contingent reinforcement of the response results in the alteration of a cell that mediates the expression of that response. Conditioning occurs through a modulation of the membrane properties of this single cell. Thus, modifications made to individual neurons (via intrinsic membrane properties and synapses) can account for both types of associative learning phenomena.

See also: Classical Conditioning, Neural Basis of; Ion Channels and Molecular Events in Neuronal Activity; Long-term Depression (Cerebellum); Long-term Depression (Hippocampus); Long-term Potentiation and Depression (Cortex); Long-term Potentiation (Hippocampus); Memory: Synaptic Mechanisms; Neural Plasticity; Neurotransmitters; Synapse Formation; Synaptic Efficacy, Regulation of; Synaptic Transmission

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F. D. Lorenzetti and J. H. Byrne

Asymmetry of Body and Brain: Embryological and Twin Studies

An individual's behavior is generated and modulated by the structure and function of the brain and body. The nervous system, which becomes the physical substratum of human cognitive processes, is formed during embryogenesis. During life, environmental stimuli are perceived, processed, and eventually manifest as behavior through the action of the brain and body. Thus, the structure of the body in general, and the brain in particular, are crucial factors in behavior and psychological processes. Therefore, an understanding of the embryonic processes which pattern the human organism is crucial to a complete understanding of cognition and behavior. Because of the ease of experimentation on animal embryos, and the high evolutionary conservation of molecular embryonic mechanisms from invertebrate animals through man, studies in animal embryos have shed much light on how the complex structure of the organism is formed during embryonic development.

1. Concepts in Molecular Embryology

The complex biochemical events which create an organism from a single fertilized egg produce intricate pattern on many scales, from the molecular to the organismic. This is accomplished through complex

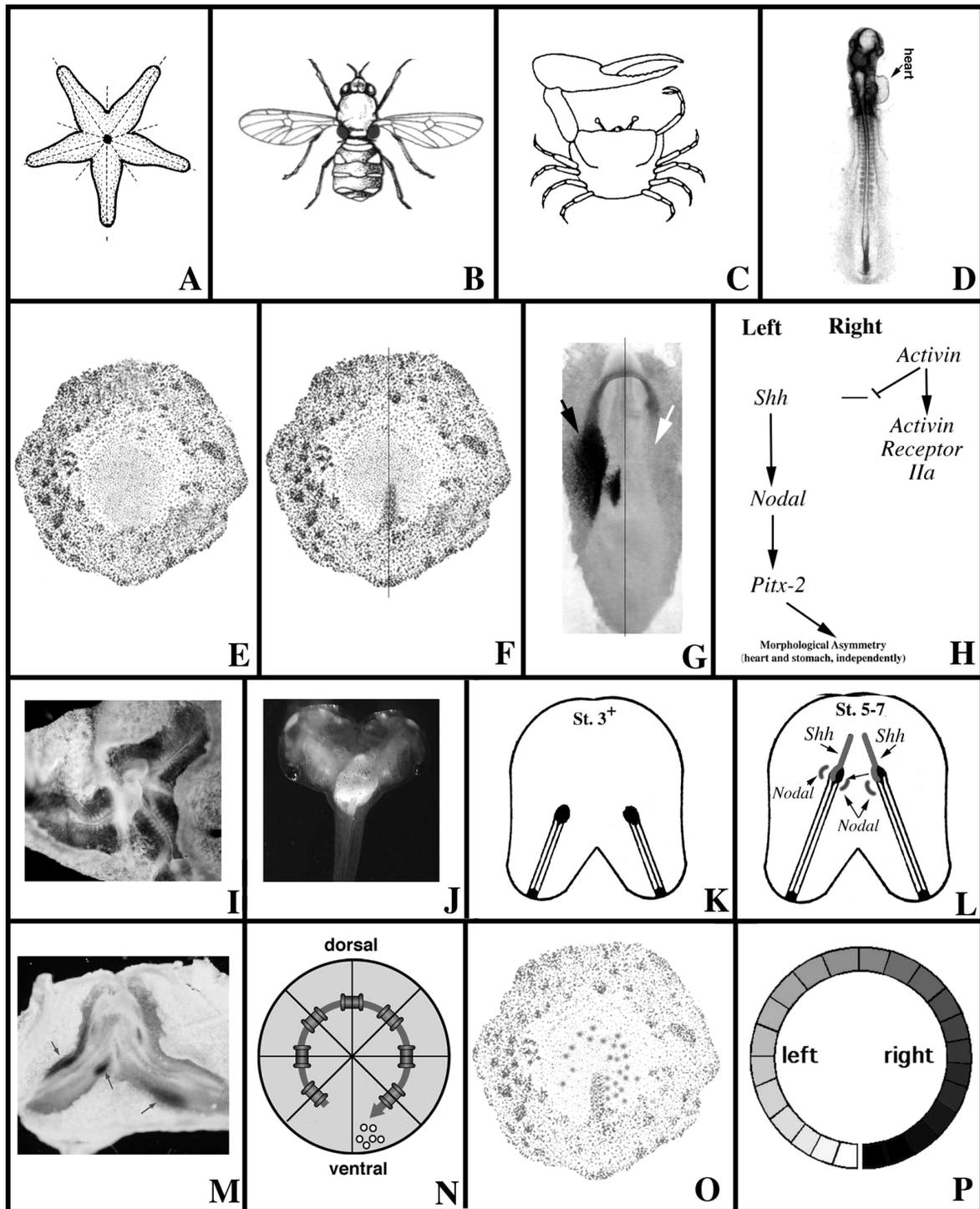


Figure 1
Caption on next page

programs of gene expression which are turned on and off as the egg begins to divide and grow. The cells which are formed as the result of this proliferation have different fates in the embryo, in that they take up different positions and biochemical functions. The genes and maternal products stored in each of the embryo's cells are transcribed into mRNA and translated into proteins which can perform physiological functions or regulate the expression of other genes. Thus, the embryo is a complex dynamical system where a precisely orchestrated interplay of information and materials takes place to generate an organism with a well-defined shape.

2. Left-Right Asymmetry

The most basic aspect of any organism's structure is the large-scale symmetry of the body plan (see Fig. 1(A)–(D)). While some invertebrates possess chirality (snail shells), radial symmetry (sea anemones), or no symmetry at all (sponges), the vertebrate body plan is bilaterally symmetric (defined as having two sides, each of which is identical to its mirror reflection across a midline axis of symmetry). While the general plan of the human body and nervous system is bilaterally symmetric, it contains important and consistent asymmetries of the brain as well as visceral organs such as the heart. The normal human anatomy features lungs which are trilobed on the right and bilobed on the left, a left-pointing cardiac apex and aortic arch, a right-

sided liver and gall-bladder, and a left-sided stomach and spleen (Casey and Hackett 2000, p. 32). In particular, lateralization of the brain is involved in many aspects of higher mental function such as speech (Corballis 1983).

The left-right (LR) axis itself follows automatically from the definition of the anterior-posterior (AP) and dorsal-ventral (DV) axes, as it is perpendicular to both; however, consistently imposed asymmetry across it is fundamentally different from patterning along the other two axes. First, while the AP and DV axes can be set by exogenous cues such as gravity, or sperm entry point, there is no independent way to pick out the left (or right) direction, since no obvious macroscopic aspect of nature differentiates left from right. This problem can be most acutely felt by imagining trying to explain to someone using only words which hand is the 'Left' hand: unless an asymmetric object exists to which one can refer, it is an extremely difficult task.

Second, all normal members of a given species are asymmetrical in the same direction (e.g., the heart is always on the same side in normal individuals). However, animals with complete mirror reversal of internal organs can arise (*situs inversus*) and are otherwise phenotypically unimpaired. Thus, while it is possible to come up with plausible evolutionary reasons for why organisms might be asymmetric in the first place (optimal packing of viscera, etc.), there is no obvious reason for why they should all be asymmetric in the same direction. It is, after all, much easier to

(A)–(D) *Symmetry types in the animal kingdom*: starfish have a fivefold radial symmetry (A); some insects such as *Drosophila* are bilaterally symmetric (B); Interestingly, some invertebrates such as crabs have a bilaterally symmetric bodyplan with conspicuous asymmetries such as claws (C). The vertebrate body plan is also bilaterally symmetrical, but contains conserved asymmetries of the viscera and heart (D). (E)–(I) *Left-right asymmetry in chick embryos*: the early chick embryo is a flat, radially symmetric two-layer disk of cells (E). The radial symmetry is broken into a bilateral symmetry by the appearance of the primitive streak at one point on the periphery. As the streak grows away from the periphery, its base becomes the posterior end of the embryo, while its tip becomes the anterior, and will induce the formation of the head and other nervous structures (F). Several genes have asymmetric expression patterns in early embryos; for example, the gene *Nodal* is expressed in two domains on the left side of the midline, shown here in the chick embryo (G). The asymmetric genes function in a pathway (H): activin on the right side inhibits the expression of *Shh*, which is then present only on the left. *Shh* induces expression of *Nodal* (only on the left side), which induces *Pitx-2*, and then transduces this information to the forming heart (I) and viscera. (J)–(L) *Conjoined twinning and asymmetry*: conjoined twins occur in embryos of chick (such as the triplets in panel I), frog (J), and other animal models. Human twins which are joined at the midline (J) are known to often exhibit disturbances of laterality. In the chick, conjoined twins sometimes occur by the appearance of two primitive streaks which begin far apart in the embryonic field (K) but then grow together with time. As the tips of the streak near each other, the expression of *Shh* on the left side of the tip of the primitive streak can induce an ectopic nodal domain on the right side of the left twin (L). This is observed in spontaneous twins which are examined for expression of nodal (M); such twins show laterality disturbances in the left twin because of the extra nodal domain on the right side. (N)–(P) *Gap junctions and asymmetry*: gap junctions are tunnels formed by connexin proteins on either side of the membrane of two opposing cells. In early frog embryos, radial patterns of open gap junctions allow the traversal of small molecular signals (morphogens) across embryonic fields; these molecules then accumulate on one side of a junctional barrier on the ventral midline (N). A very similar process occurs in the chick (O), where the junctional paths allow morphogens to flow across the blastoderm to accumulate on one side of the primitive streak. This process is schematized in (P): junctional paths allow signals to traverse embryonic fields to preferentially accumulate on one side of the midline, thus converting a cell-level asymmetry (which drives one-way transfer through gap junctions) to an embryo-wide asymmetry

imagine a developmental mechanism for generating asymmetry (such as positive feedback and amplification of stochastic biochemical differences) than for biasing it to a given direction. The left–right axis thus presents several unique and deeply interesting theoretical issues.

Normal asymmetry (*situs solitus*) can be perturbed in one of several ways, and various human syndromes recapitulate all of these (Burn 1991, Winer-Muram 1995). *Situs inversus* is a complete mirror image inversion of asymmetry, and does not usually cause complications because all interconnections are made properly. However, isomerism (a loss of asymmetry, where an embryo has two left or two right sides, which can result in polysplenia or asplenia, a midline heart, etc.) and heterotaxia (a loss of concordance, where each organ makes an independent decision as to which side it will go towards) are associated with serious medical complications.

3. The Molecular Basis of Asymmetry

Molecular embryology has made great strides in understanding the patterning of the antero-posterior and dorsoventral axes. However, prior to 1995, very little was known about the molecular mechanisms which give asymmetric cues to the left and right sides of the body. A large catalog of asymmetries in the animal kingdom was available (Neville 1976). Besides the human syndromes which exhibited alterations in laterality, a variety of mouse mutants existed which displayed various laterality phenotypes. However, the nature of the mutations responsible for these effects was unknown. It had been observed that a variety of drugs was able to induce asymmetry phenotypes in embryos (Levin 1997), and timing experiments using these drugs indicated that processes which lead to asymmetry function very early in embryonic development (prior to neural tube formation).

The identification of a chicken gene, *Sonic Hedgehog* (*Shh*), cloned in 1993 because of its role in limb and neural tube patterning (Riddle et al. 1993) turned out to be pivotal in understanding left–right patterning. The chick embryo begins as a flat disk only three cell layers thick and is radially symmetric (Fig. 1(E)). However, soon afterwards a structure appears which is called the primitive streak (see Fig. 1(F)). This groove of special cells which are undergoing gastrulation is common to mammals and many other types of embryos, and marks the breakage of symmetry from the radial to the bilateral, since it defines the midline of the embryo, and sets up the antero-posterior axis. When the chick embryo at this stage is examined for the presence of mRNA of the gene *Shh* by a procedure which deposits blue stain wherever the gene is active, it is seen that this gene is only transcribed on the *left* side of the tip of the primitive streak, and not the right; this is even more obvious for a gene

called *Nodal*, which is expressed in a wide domain on the left flank. The identification of several other asymmetric genes followed, and now a variety of genes is known which are active on the left or right sides (Levin 1998b). More importantly, by a variety of experiments involving artificial retroviruses, gene cloning and misexpression, and transgenic mouse technology, it was shown that these genes function in a pathway: they turn each other's expression on and off in a spatially and temporally specific manner to give each side of the body an identity. The presence of the *Shh* gene defines the left side as left; its absence defines the right side. These gene cascades provide information which is interpreted by asymmetric organs such as the heart to enable them to know which direction is left and which is right (summarized in Fig. 1(H)). For example, it was shown that if the normally left-sided *Shh* expression is artificially induced on the right side as well (thus producing an embryo both of whose sides think they are 'left'), the heart forms properly, and loops correctly in 50 percent of the cases, but loops to the opposite side in the other 50 percent. In effect, the heart (and other viscera) must choose randomly when presented with conflicting information. The details of the molecular cascade of asymmetric genes can be seen in reviews such as Burdine and Schier (2000), Fujinaga (1996), and Wood (1997).

Several of these genes are of particular interest to behavioral science, as they presage signals for the determination of brain laterality. For example, the chick gene *Cerberus* is expressed on the left side of the embryonic head, shortly after neural tube closure (Zhu et al. 1999). The same is true of genes such as *Pitx-2* in zebrafish embryos (Essner et al. 2000). It should be kept in mind that though most of this data comes from animal models, there is a high degree of conservation of embryonic mechanisms, and these gene cascades are very likely to be crucial in patterning all vertebrates including man (Casey and Hackett 2000).

4. Conjoined Twins and Laterality Defects

The identification of asymmetrically expressed genes whose protein products specify the spatial asymmetry of the viscera and brain made it possible to explain, on a molecular level, an observation which had been found in conjoined human twins. Twins and the twinning process have had a relevance for laterality research ever since the tantalizing experiments of Spemann (Spemann and Falkenberg 1919). It has been noted (Burn 1991, Morrill 1919, Newman 1916, Schwind 1934, Winer-Muram 1995) that conjoined twins in human beings, mice, and frogs tend to exhibit laterality defects. Animal models of twinning have been instrumental in understanding this defect in embryogenesis (Fig. 1(I), (J)).

In reviewing the human literature on conjoined twins, it was observed that parapagus and thoracopagus twins (twins joined at the chest or side-to-side) tend to exhibit *situs* abnormalities (Levin et al. 1996); these are twins thought to originate from two adjacent embryonic streaks developing side by side, either in parallel or obliquely (schematized in Fig. 1(K)). Guided by the LR pathway, Levin et al. (1996) examined the expression of the asymmetric genes in analogously positioned chick twins and proposed two models explaining laterality defects found in conjoined twins. These are both based on molecules in the LR pathway crossing some distance in the blastoderm and affecting the conjoined embryo. The precise details of geometric arrangement and timing determine which members of the LR cascade affect the twin, and thus control which twin exhibits the *situs* anomaly.

For example, when primitive streaks arise far apart, but grow towards each other during gastrulation (Fig. 1(K), (L)), *Shh* expression proceeds normally in both twins on the left side of the tip of the primitive streak. However, during head-fold stages, the *Shh* expression of the right twin induces not only the normal left-sided *Nodal* expression, but also induces aberrant *Nodal* expression on the right side of the left twin (Fig. 1(L)). When head-fold stage spontaneous chick twins with oblique streaks are examined for *Nodal* expression (Fig. 1(M)), as predicted it was seen that the right twin has *nodal* expression only on the left side (i.e., normal expression), while the left-most twin has expression (black arrows) on both the left and right sides (which leads to laterality defects). Thus, studies of twins in model systems such as the chick have provided a crucial arena in which to test molecular models which explain clinical findings in human teratology.

5. Nonconjoined Twins and Asymmetry

The models discussed above present plausible explanations of laterality defects in conjoined twins. There is, however, an interesting set of observations which suggest that they do not tell the whole story, and that even in mammals, chirality is determined as early as the first few cell divisions, and certainly before the streak appears. Nonconjoined monozygotic twins, while not exhibiting the kinds of visceral laterality defects that occur in conjoined twins, do manifest many subtler kinds of mirror-image asymmetry ('bookend' or enantiomer twin pairs), where some characteristic is left-sided (or counterclockwise) in one twin but right-sided (or clockwise) in the other.

Pairs of such twins have been noted to present such mirror asymmetries in hand preference, hair whorl direction, tooth patterns, unilateral eye and ear defects, and even tumor locations and undescended testicles (Beere et al. 1990, Carton and Rees 1987, Cidis et al. 1997, Gedda et al. 1981, Morison et al. 1994, Newman et al. 1937, Townsend and Richards

1990, Yager 1984). Most healthy, nonconjoined twins presumably result from separation of cleavage, morula, or early blastocyst stage embryos (James 1983). Thus, some chiral information may be present in the very early mammalian embryo, manifesting itself in hair whorls etc. if the cells are separated at an early stage. In contrast, the asymmetry of the major body organs seems to be unspecified (or at least plastic enough to be respecified) at those stages, and is developed correctly for both monozygotic twins. This may be related to the fact that heterotaxic reversals in hair whorls and tooth patterns would not be expected to be disadvantageous, while discordant *situs* for internal organs clearly is subject to negative evolutionary pressure.

6. Upstream of Asymmetric Genes

Pathways of asymmetric gene expression beg the question: what determines the sidedness of the first asymmetric gene? The very first step of asymmetry at the cellular level is presently unknown, but is thought to perhaps involve a chiral (handed) molecule which is tethered with respect to the other two axes, and has an activity which distinguishes left from right (Brown and Wolpert 1990). Interestingly, the identification of such a mechanism would still leave an important question unanswered, because for a cell, knowing which direction is left vs. right is a very different problem than knowing which side of the midline it is on. Knowing its position relative to the midline is crucial for proper expression of asymmetric genes. Thus, what is needed is a mechanism for transducing left-right directional information at the level of a single cell into embryo-wide fields of asymmetric gene expression.

Recent experiments have shown that a system of cell-cell communication exists by means of which the two sides of very early embryos decide which side is to be the right side and which is to be the left (Levin and Mercola 1999). Such a system involves cell-cell channels known as gap junctions, through which small molecular signals can pass (Fig. 1(N)). Once crucial LR decisions are made in a small group of cells, this information can be distributed to the whole organism through circumferential paths of open gap junctions (Fig. 1(O), (P)). Twin embryos will be crucial in testing these models because the gap junction models make specific predictions about what should happen to circumferential paths when more than one primary axis exists in an embryonic field (as in conjoined twins growing side by side, in parallel).

7. Twins and the Origin of the Primary Axis

Bilateral asymmetry presupposes the existence of a midline axis, across which symmetry or asymmetry is observed. In the chick this is accomplished by the

primitive streak growing out of a specific point on the periphery of the blastoderm, and thus breaking radial symmetry into bilateral symmetry. However, it is known that when suitably stimulated, any point on the periphery is able to serve as the site of streak initiation. Yet, in the great majority of embryos, only one primary axis is observed (singleton embryos). What is responsible for the appearance of one and only one streak, when many points could potentially initiate streaks?

Research has showed that at very early stages, many chick embryos in fact consist of more than one primary axis, and are conjoined twins. Interestingly, at this crucial stage of embryogenesis, the streaks secrete a streak-inhibitory factor in an attempt to suppress the appearance of other streaks (Levin 1998a). In most embryos, this competition results in the primary dominant streak inhibiting other streaks and in fact causing the extra streaks to dissolve. Thus, twinning illustrates the mechanisms underlying the control of the number of primary axes in the embryonic field—a key component of embryogenesis.

8. *Prospects for the Future*

The phenomenon of twinning provides crucial insight into the earliest steps of embryonic pattern formation; luckily, twins can be experimentally induced in various systems with ease (Fig. 1(I), (J)). Conjoined animal twins allow researchers to answer questions regarding mechanisms by which primary axes arise from a competent embryonic field. Moreover, conjoined twins are the perfect system in which to characterize paths which facilitate, and barriers which block, the flow of left–right information during embryogenesis. This information is of vital importance in understanding normal mechanisms of embryonic development.

Nonconjoined twins provide a special challenge to molecular embryology. The bookending phenomenon, which displays a conservation of chirality in nonconjoined twins, provides tantalizing clues about the very first steps in the generation of embryonic asymmetry, and has implications for evolution of the vertebrate body plan. The data suggesting that the head and brain have a system of asymmetry determination distinct from the rest of the body have far-reaching implications for cognitive science. Progress on this issue will be a key part of a molecular understanding of the embryonic development of systems which generate and shape human behavior.

See also: Behavioral Genetics: Psychological Perspectives; Brain Asymmetry; Comparative Method, in Evolutionary Studies; Genetic Studies of Behavior: Methodology; Genetic Studies of Personality; Intelligence, Genetics of: Cognitive Abilities

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M. Levin

Atomism and Holism: Philosophical Aspects

In the philosophy of the social sciences, atomism is the view that human beings can be thinking, rational beings independently of social relations. Holism, by contrast, is the view that social relations are essential to human beings insofar as they are thinking, rational beings. This article first provides an overview of different sorts of atomism and holism (see Sect. 1). It then briefly sketches the historical background of these notions in modern philosophy (Sect. 2). The main part is a systematic characterization of atomism and holism (Sect. 3) and a summary of the most important arguments for both these positions (Sect. 4).

1. Types of Atomism and Holism

If one speaks of atomism or holism, one has to specify with respect to what atomism or holism is claimed. Atomism with respect to one thing or aspect can go with holism with respect to another thing or aspect, and *vice versa*. In the social sciences, the discussion on atomism vs. holism focuses on the question whether social relations to other humans are essential to human nature. The question thus is whether society in the sense of a social community of human, thinking beings is an atomistic or a holistic system. The question is neither whether a human being can exist in the biological sense without social relations nor whether a human being is dependent on social relations for maintaining a fully satisfactory human life. The point at issue is whether a human being is dependent on social relations to other humans insofar as he or she is a thinking, rational being. Since, on most accounts, thought in the full sense of the term as exhibited by adult human beings is tied to rationality constraints and since rational agency, including moral agency, presupposes thought, the point at issue can be formulated thus: are social relations necessary for a human

being to have thoughts with a determinate conceptual content? Social atomism is the thesis that an individual considered in isolation can have thoughts with a determinate conceptual content. Social holism, by contrast, is the thesis that social relations are essential for a human being in order to have thoughts with a determinate conceptual content. Social holism thereby implies that having thoughts is tied to speaking a public language; social atomism does not have such an implication.

The discussion on atomism vs. holism concerns not only the conditions under which humans can have thoughts; it extends also to aspects of thoughts. The most important issue in this respect is the question whether meaning is atomistic or holistic. Semantic atomism is the thesis that each thought or sentence has a meaning independently of other thoughts or sentences. Semantic holism, in reverse, is the thesis that the meaning of a thought or a sentence consists in its inferential relations to other thoughts or sentences in a system of thoughts, a theory, etc. There is a middle position, namely semantic molecularism. This is the thesis that only some particular inferential relations to other thoughts or sentences, most prominently the analytic ones, constitute the meaning of a thought or a sentence.

Atomism and holism are put forward with respect to further aspects of thoughts. Confirmation atomism is the thesis that thoughts or sentences can be empirically confirmed or disconfirmed one by one. Confirmation holism, by contrast, is the thesis that only a whole system of thoughts or a whole theory can be confirmed or disconfirmed by experience. Consequently, if a conflict between theory and experience occurs, there are several possibilities for adapting the theory to experience. Justification atomism is the thesis that there are some thoughts or sentences which can be justified without referring to other thoughts or sentences. These thoughts or sentences are the foundation of knowledge. Justification atomism is, therefore, known as foundationalism. Justification holism, by contrast, is the thesis that the justification of any thought or sentence consists in relations to other thoughts or sentences. Justification holism is, therefore, known as coherentism: the justification of a thought or a sentence is its being integrated into a coherent system of thoughts or sentences. Although there are arguments which link all these sorts of atomism or holism together, endorsing any one sort of atomism or holism does not logically commit one to endorse any other sort of atomism or holism as well.

2. The Historical Background of Atomism and Holism

The issue of atomism vs. holism in the social sciences is linked closely with philosophical reactions to what is perceived as the methodology of modern physics.

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