The Controversy over Cultural Group Selection. In 2012 the Canadian psychologist and popular science writer Stephen Pinker (1954–) penned a strong critique of the idea that culture can be subject to group selection, indeed that it can be conceived of as evolving in the same sense as genes at all. A considerable number of commentators on Pinker's essay supported his attack, while others defended cultural evolution and cultural group selection.

SEE ALSO *Animal Behavior; Modern Evolutionary Synthesis; Natural Selection; Origin of Species; Origin of Species, Reaction to.*

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Kathryn Demps
Assistant Professor of Anthropology
Boise State University

Peter Richerson
Distinguished Professor Emeritus
University of California, Davis

GROWTH FACTORS

The Nobel Prize in Physiology or Medicine was awarded to the Italian neurologist Rita Levi-Montalcini (1909–2012) and the American biochemist Stanley Cohen (1922—) in 1986 for their discovery of growth factors. Working together in the laboratory of the German-American embryologist Viktor Hamburger (1900–2001) at Washington University in St. Louis, Missouri, Levi-Montalcini and Cohen published numerous papers about the discovery, isolation, and physical properties of the first two growth factors to be identified: nerve growth factor (NGF) and epidermal growth factor (EGF). Their findings led many other research groups to follow in their footsteps and explore new growth factors. Since the discovery of NGF by Levi-Montalcini and EGF by Cohen, dozens of growth factors have been isolated and characterized.

NERVE GROWTH FACTOR

In 1947 Levi-Montalcini was invited to join Dr. Hamburger to repeat previous experiments performed by one of Hamburger's former students, the American zoologist and anatomist Elmer Bueker (1903–1996). In an effort to study the influence of tumors on the development of the lumbosacral nervous system, Bueker implanted mouse sarcoma 180 (a specific type of malignant tumor) or other tumor fragments into chick embryos after removing hindlimb tissue. As a result, he observed spinal ganglia enlargement and penetration of the tumor by nerve fibers of the

Rita Levi-Montalcini. *Dr. Rita Levi-Montalcini, professor of Zoology, in her lab at Washington University, about 1963.* BERNARD BECKER MEDICAL LIBRARY, WASHINGTON UNIVERSITY SCHOOL OF MEDICINE

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host. His initial hypothesis was that the observed tumor effect was mediated by innervating nerve fibers.

Levi-Montalcini used a silver impregnation technique—first developed by the Spanish pathologist and neurologist Santiago Ramón y Cajal (1852–1934) and later refined by the Brazilian embryologist Nylceo Marques De Castro (1919–1970)—to further characterize the relationship between nerve fibers and neoplastic cells as well. She noted that sarcomas 180 and 37 produced growth-promoting agents that could stimulate the growth of sympathetic and some sensory fibers, but not motor fibers. In 1952 she studied the effects of mouse tumor transplantation on the nervous system *in vivo* and noticed that nerve fibers did not enter the tumor until the sixth day of development and that a large portion of the nerve bundles did not contact any of the tumor cells. As a result, she suggested that sarcomas 180 and 37 may release an agent that selectively stimulates the growth of both late-differentiating sensory cells and sympathetic ganglia. Up to this point, however, the chemical nature of this agent and its mode of action remained unknown.

Since previous experiments gave no clue as to whether the growth-promoting agent acted directly or indirectly on the ganglia, Levi-Montalcini devised a new hanging-drop bioassay to help identify the factor. She incubated spinal or sympathetic ganglia from chick embryos with a tumor fragment placed 1-2 millimeters away. In response to sarcoma 180 or 37, there was a large outgrowth of nerve fibers as early as 12 hours after initiation of the experiment. She thus concluded that the increase in nerve fiber density and fiber outgrowth were due to a diffusible agent because the tumor does not require contact with the ganglion or nerve fibers to exert its effects. The next step was to characterize and localize the source of this growth-stimulating factor.

In 1953 Cohen joined the research group in St. Louis. He exposed the chick sensory ganglia to a crude tumor extract and, remarkably, still observed nerve fiber outgrowth. To identify the intracellular location of the growth-promoting agent, he employed a differential centrifugation method and found that almost all of the activity resided in the microsomal fraction (particles originating in the cell's cytoplasm). With the use of various biochemical assays, he concluded that the active material was heat-labile (susceptible to deactivation by heating) and nondialyzable (not able to be separated by passage through a semipermeable membrane). To confirm the active agent was a protein, Cohen added phosphodiesterase (an enzyme) purified from snake venom to destroy nucleic acids. To his surprise, the venom induced a huge increase in nerve fiber outgrowth. He and Levi-Montalcini concluded that the behavior observed in the venom was similar to that of the "protein fraction" isolated from sarcoma 180.

Cohen proceeded to purify the growth-promoting factor from venom and learned that it was one thousand times more potent than their purest tumor fraction. Levi-Montalcini and Cohen then injected the venom into the yolk of embryos, which resulted in a growth-stimulating effect on the sensory and sympathetic ganglia of the embryo, following exactly the effects induced by mouse sarcomas. By 1959 he would more properly purify and characterize this ner NGF from both mouse sarcoma 180 and from snake venom and confirm that they are both protein. It was not until 1971 that the NGF from mouse submaxillary gland was sequenced by the American molecular biologists and biochemists Ruth Angeletti and Ralph Bradshaw (1941–). Since its discovery, NGF has also been shown to play a role in apoptosis (programmed cell death), neurodegenerative diseases, and various psychiatric disorders.

Epidermal Growth Factor. After discovering and purifying the NGF in snake venom, Cohen pondered the connection between nerve growth, tumors, and snake venom. Knowing that snake venom came from modified salivary glands, he decided to purify extracts from the male mouse salivary gland. Cohen and Levi-Montalcini characterized both the salivary growth-promoting protein and its antiserum in a variety of models. The addition of the salivary gland extract into chick embryos resulted in hypertrophy (increased cell size) and hyperplasia (increased cell number) of the sympathetic ganglia and an increase in nerve fibers. The injection of the purified salivary extract into newborn mice results in increased sympathetic ganglia and cortisone-like effects: stunted growth, failure of hair to grow, precocious opening of their eyes, and early eruption of their teeth. Cohen observed that injection of the antiserum of this purified protein into newborn animals, including mice and rabbits, resulted in a high degree of atrophy. Upon comparing the chemical nature of the NGF and the salivary extract, along with other evidence gained from antiserum and *in vivo* experiments, they concluded that both factors are proteins, but are in fact different growth factors.

Cohen isolated the protein responsible for the earlier development of the eyelids and incisors in mice in 1962. Using histological analysis, he found that the protein enhanced epidermal keratinization and increased the overall thickness of the epidermis. Within the next decade, he discovered that this growth factor could stimulate epidermal proliferation and even determined the primary structure of the protein using Edman degradation (a method used to determine the amino acid sequence of peptides). He spent much of the remainder of his career examining the metabolic effects of EGF, purifying human epidermal growth factor (hEGF), and used radiolabeling to determine the mechanism of EGF.

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Fibroblast Growth Factor. After the initial findings of Levi-Montalcini and Cohen, several research groups looked for other existing growth factors. Most mammalian cell lines did not survive when supplemented with only amino acids, vitamins, and glucose—serum was required. But what was in serum that stimulated cell growth? The mouse cell line 3T3 was a popular model during this investigation; the addition of calf serum to confluent, non-dividing cells resulted in increased RNA synthesis, DNA synthesis, and cell division in select cells. In 1970 John L. Jainchill and George J. Todaro alcohol-precipitated serum and found that the supernatant alone could not stimulate cell division in 3T3 cells. When the pellet was reconstituted into the precipitated fraction, the cells divided. Evidence that growth factors in serum were essential for cell proliferation was increasing but attempts to purify growth factors from serum proved to be difficult.

In 1973 the Brazilian biologist Hugo Armelin (1939–), then at the University of California at San Diego, showed that pituitary extracts had a similar potent growth-promoting activity in a 3T3 cell line of mouse fibroblasts suggesting that the pituitary gland was a source of growth factor(s). This was soon called fibroblast growth factor (FGF) and was purified from bovine pituitary by Denis Gospodarowicz. Interestingly, it was shown that a substance isolated from bovine pituitary glands could induce growth in a rat ovarian cell line. Since the discovery and purification of FGF in the early 1970s, over twenty other members of the FGF family and additional functions, such as wound healing, embryonic development, and the promotion of certain types of cancer, have been identified.

Insulin-like Growth Factors. The path to discovering insulin-like growth factors began in 1957 when W. D. Salmon Jr. and William Daughaday (1918–2013) proposed that a circulating serum factor, termed sulphation factor (SF), mediated the action of growth hormone (GH) on skeletal tissue *in vivo*. Several groups tried to identify and purify this mysterious factor from human serum. In 1963 glucose uptake measurements and net gas exchange of adipose tissue measurements performed by E. R. Froesch and colleagues led to the observation that an insulin-like activity that could not be suppressed by insulin antibodies (“non-suppressible insulin-like activity,” or NSILA) existed in human serum. In 1971 K. Hall and K. Uthne realized that the SF activity and NSILA were inherent in the same molecule—it was not possible to separate the two during purification. Within the next year, a new designation of “somatomedin” was proposed.

The field changed drastically when Hall purified the polypeptide somatomedin A (SMA) in 1972 and J. J. van Wyk and colleagues purified somatomedin C (SMC) in 1972. In 1976 E. Rinderknecht and R. E. Humbel purified two homogenous polypeptides from serum with both NSILA and cell-growth promoting activity. Named NSILA-I and NSILA-II, both components were single-chain basic polypeptides with a specific activity sixty times lower than that of insulin, but differed in amino acid composition. Later, however, these were re named insulin-like growth factor I (IGF-I) and insulin-like growth factor II (IGF-II), respectively. In addition, a somatomedin-like polypeptide called multiplication-stimulating activity (MSA) was purified from cultured rat liver by S. P. Nissley and M. M. Rechler in 1978.

Within that same year, the primary amino acid sequence of both IGF-I and IGF-II were solved. Thanks to this advancement, it was confirmed that SMC’s sequence was identical to IGF-I, SMA was a deaminated form of IGF-I (i.e., the IGF-I molecule with an amino group removed), and MSA was actually IGF-II. The initial sulphation factor that could mediate the effects of GF discovered in 1957 was actually IGF-1. After years of investigation and nomenclature changes, the family of insulin-like growth factors was finally established. It is now known that these growth factors are structurally similar to insulin and have a wide range of biological effects including a role in embryonic development, growth regulation in of a variety of tissues, and even tumorigenesis.

Transforming Growth Factors. By the late 1970s, it was clear that the growth of normal cells was dependent on growth factors present in tissue fluids. Malignant cells, however, required far less assistance from exogenous growth factors for growth in cell culture. One explanation for this phenomenon was offered in 1980 by the “autocrine secretion” hypothesis. The idea was that transformed cells require less exogenous growth factors because of an increased production of endogenous growth factors. This was thought to be the result of transforming growth factors (TGFs) which cause loss of density-dependent inhibition and overgrowth of cells in a monolayer, change in cellular shape, and an acquirement of anchorage independence.

Prior to this hypothesis, George Todaro and Joseph De Larco suggested that the murine sarcoma virus-transformed mouse fibroblasts produced and released a sarcoma growth factor (SGF) to carry out its transforming actions on normal cells. SGF was found in the conditioned medium and was thought to be in the family of TGFs because it could induce anchorage-dependent cells to act as anchorage-independent cells as assayed by the soft agar growth assay. In 1980 two polypeptides were extracted and purified from tumor cells growing both in culture and *in vivo* using the acid/ethanol method by A. B. Roberts and colleagues and were thought to be similar to the previously isolated SGF.

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RITA LEVI-MONTALCINI

Born on April 22, 1909, to a loving Jewish family, Rita Levi-Montalcini was raised in Turin, Italy. Her father believed in traditional Victorian customs and discouraged his daughters from pursuing professional careers because it would interfere with the duties of being a wife and a mother. Eventually, Levi-Montalcini convinced her father to let her enter medical school, where she studied under Giuseppe Levi (1872–1965), a famous Italian histologist. She graduated with a degree in Medicine and Surgery in 1936 and enrolled in a specialization in neurology and psychiatry. In 1938 the Italian Fascist leader Benito Mussolini (1883–1945) issued a manifesto that stripped away several civil rights, including professional positions, from non-Aryan Italian citizens. Shortly after, Levi-Montalcini returned home to Turin and, inspired by Viktor Hamburger's work on limb extirpation in chick embryo, built a small laboratory in her bedroom. Giuseppe Levi joined her as an assistant in 1940 after escaping the Nazi invasion of Belgium. During World War II, however, Levi-Montalcini and her family were forced to flee and eventually live underground in Florence until 1944, when the Anglo-American armies expelled the Germans. Levi-Montalcini worked as a medical doctor at a refugee camp before returning to her academic position at the University of Turin.

In 1947 she accepted an invitation to join Viktor Hamburger's laboratory at Washington University in Saint Louis where she carried out her groundbreaking studies leading to the identification of NGF. Levi-Montalcini also established a research unit in Rome (1962), became a director of laboratory cell biology of the Italian National Council of Research (1978), supported educational programs and scholarships, particularly for women in Africa, and received numerous accolades, including the appointment to the Italian Senate for Life in 2001. She died in Rome on December 30, 2012 at the age of 103.

A related set of intracellular TGFs from non-neoplastic tissues including adult mouse skeletal muscle, heart, liver, kidney, brain, and submaxillary gland were purified in 1981. Importantly, transforming activity in soft agar of crude extracts was lost when subjected to gel filtration column analysis; the activity could be recovered when the two separate fractions of the column were reconstituted by the American molecular biologist Anita Roberts (1942–2006) and colleagues. One fraction (later termed transforming growth factor-α, TGFα) could only induce a small number of cell colonies in the soft agar and competed with EGF receptor binding. The second fraction (later termed transforming growth factor-β, TGFβ) induced large colonies of cells in soft agar and did not compete with EGF in the receptor binding assay. TGFβ was subsequently purified and characterized from human placenta, human platelets, and bovine kidney. Further study revealed that TGFβ played a variety of additional roles including stimulation of angiogenesis (new blood vessel growth) and collagen formation.

THE HUNT FOR NEUROTROPHIC FACTORS

Neurotrophins are a unique family of closely related polypeptide growth factors that play a role in the proliferation, differentiation, survival, and death of neurons. After the discovery of NGF in the 1950s, many research groups were interested in finding other growth-promoting factors that targeted nerve cells or neurons. It was not until 1982, however, that the second neurotrophin was identified by Yves Barde in the laboratory of the Swiss neurobiologist Hans Thoenen (1928–2012) at the University of Basel in Switzerland. Initially, Thoenen studied the "how" of nerve growth factor and played a major role in the initial studies of the retrograde axonal transport of trophins. Subsequently, Thoenen and his colleagues aimed at discovering other neurotrophic factors and eventually found several including brain-derived neurotrophic factor, ciliary neurotrophic factor, and neurotrophin-6. His research group led the way for finding new members of the neurotrophin family. "There is no reason to think that BDNF and NGF should be the only members of a family of neurotrophic proteins … it is hoped that the structural features common to both NGF and BDNF can be used to aid the discovery of other members" (Leibrock et al. 1989, p. 152).

Brain-derived Neurotrophic Factor. In initial studies performed in Thoenen's laboratory in 1978 involving cultured C-6 glioma cells, a polypeptide that could support survival and process formation in dissociated neurons from dorsal root ganglia of chick embryo was identified. It was confirmed to be a factor other than NGF because its effect was still observed when antibodies to NGF were added to the media. In a separate experiment, chicken sensory neurons were grown in glioma cell conditioned medium (GCM) and the survival rate of cells dramatically increased; the survival rate increased even further with the addition of NGF. This confirmed

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that a growth factor had been released into the media, but what was it? Shortly thereafter, the neurotrophic factor was purified from pig brain and characterized using basic biochemical techniques in Thoenen's laboratory. It could support the survival and fiber outgrowth of cultured embryonic chick sensory neurons and had unique antigenic and functional properties distinct from NGF. It was later named brain-derived neurotrophic factor (BDNF). Since its discovery, it has been implicated in neurogenesis, modulation of pain, epilepsy, and several neurodegenerative diseases.

In 1989 Thoenen's group was able to determine the full primary structure of BDNF and give evidence to its existence throughout the central nervous system (CNS). They compared the amino acid sequence to that of NGF and found about 50 percent similarity, including overlap of all six cysteine residues in each protein. Thus, they discovered that BDNF and NGF were both members of a family of "neurotrophins" sharing both functional and structural characteristics. And so began the hunt for other members of this gene family.

Neurotrophin-3, Neurotrohpin-4/5, and Neurotrophin 6. During the late 1980s, the search for new members of the neurotrophin family grew exponentially. Using the similar structure of BDNF and NGF to their advantage, several groups obtained degenerative oligonucleotides from the most highly conserved regions of BDNF and NGF homology to search for additional members of this gene family. These oligonucleotides were used as primers in polymerase chain reaction (PCR) to amplify potential candidates for homologous neurotrophic factors. This technique quickly paid off when two independent groups unearthed a factor with unique neurotrophic activity (neurotrophin-3, NT-3) from mouse and rat genomic DNA libraries. Rat NT-3 shared 57 percent sequence homology with rat NGF and 58 percent with rat BDNF. It was clear that many research groups were on the same hunt because several other authors published similar findings for a variety of species within that same year. Using similar techniques, neurotrophin-4 and neurotrophin-5 were identified in 1991 but shortly thereafter researchers realized they were in fact the same growth factor and eventually assumed the name "neurotrophin-4/5" to acknowledge both discoveries. The newest member of the neurotrophin family joined in 1994 with the successful cloning of neurotrophin-6 from the platyfish *Xiphophorus maculatus*.

Ciliary Neurotrophic Factor. Studies by the molecular biologist Stephen L. Helfand in the 1970s on cultured dissociated parasympathetic neurons from ciliary ganglia found that neuronal survival increased drastically when cells were cultured with heart conditioned media (HCM), but the effect did not seem to involve the well-known NGF. This same behavior was found in a variety of other in vitro models, suggesting the existence of a putative cholinergic neuronotrophic factor (CNTF). Evidence from a research group headed by the Italian-American neuroscientist Silvio S. Varon (1924–2005) pointed out that this trophic factor was most concentrated in the intraocular region, which was later purified and renamed the ciliary neurotrophic factor. Since that time, it has been shown to play a role in glial differentiation and the survival of motor neurons. Initial studies using CNTF as a therapy for progressive motor neuropathy showed optimistic results, including prolonged survival and improved motor function in mice. Interestingly, CNTF has also been associated with leptin-deficient obesity and diabetes, having the potential to act as a therapeutic, a topic that is still being explored today.

Glial cell-derived Neurotrophic Factor. Before the discovery and purification of glial cell line-derived neurotrophic factor (GDNF) in 1993 by L. F. Lin and colleagues, several research groups reported that glial conditioned media had growth-promoting effects on dopaminergic neurons. GDNF effects the survival and morphological differentiation of dopaminergic neurons but does not increase total neuron or astrocyte numbers. The therapeutic potential of GDNF in treating Parkinson's disease, a disorder marked by the progressive degeneration of dopaminergic neurons in the CNS, was explored in rodent and primate models and showed great promise.

Amgen, a biotech company, carried out human trials which showed that monthly intracerebroventricular (ICV) catheter administration of GDNF to patients with Parkinson's disease did not improve symptoms but instead led to several adverse effects. These results were contradicted by a small, open-label follow-up study performed in 1993 (wherein both the patients and researchers were aware of the treatment given) that showed GDNF administration led to significant clinical improvement, including improved motor scores and putaminal dopamine storage with no serious side effects. In response, Amgen sponsored a double-blind trial (wherein the exact treatment was unknown to patients and researchers) with thirty-four patients to test the efficacy of GDNF. Six months later, Amgen announced that GDNF failed to demonstrate any clinical improvement in advanced Parkinson's, although the statistical analysis and interpretation of these results has been the subject of debate. Amgen halted the clinical trials, a decision supported by the US Food and Drug Administration (FDA), Health Canada, and the Medicines and UK Healthcare Products Regulatory Agency (MHRA). Additional support for Amgen's action came from both the finding of neutralizing antibodies in three participants and a toxicology study showing variable Purkinje and granule cell

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loss in the cerebellum of monkeys, although critics claim that Amgen overreacted to safety concerns and misinterpreted toxicology findings.

The decision to terminate GDNF administration was met with more controversy when Amgen denied the requests of participants who wished to continue treatment. Additionally, an autopsy of a participant of the open-labeled study who died of an unrelated heart attack revealed sprouting and regrowth of dopamine nerve fibers. Although the use of GDNF remains controversial, the effects on dopamine nerve growth are evident.

SEE ALSO *Cancer, Molecular Basis of; Cell Division Molecular Dynamics; Cell Signaling; Hormones; Neurogenesis, Adult.*

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Jacqueline A. Hubbard
PhD candidate, Department of Biochemistry and Molecular Biology
University of California, Riverside

Devin K. Binder
Associate Professor, Division of Biomedical Sciences
School of Medicine, University of California, Riverside

GULF STREAM

The Gulf Stream is a warm ocean current that starts in the Gulf of Mexico, flows through the Florida Straits and then up the eastern coast of the United States, turning out to sea near Cape Hatteras. It is a ribbon of high-velocity water that forms the boundary between the warm waters of the Sargasso Sea and the cooler waters of the coastal United States and the North Atlantic Ocean. As it moves across the North Atlantic Ocean toward Europe it branches north and south to become the North Atlantic Current and the Azores Current. It is wind driven and one of the strongest ocean currents, carrying more water than all of the rivers of the world combined. Because of its strength and broad scope it plays a key role in the global transport of heat from the equator to the poles. The Gulf Stream is just one of several so-called "western boundary currents" that exist in most ocean basins. Its warm waters allow tropical fish species to exist as far north as southern Long Island.

A typical speed at the surface is about 4 miles per hour (1.79 meters per second), fast enough to have a considerable effect on sailing vessels and a notable effect on powered ships. In fact, it was by its effects on the

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