HEALTH PSYCHOLOGY

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There are lots of things that I’d like to know, but that I don’t have the capacity to understand or the opportunity to look into. There are also things that would be nice to know, but as I don’t actually need to know these things, I don’t dwell on them. When I would say to my dog “We’ll save this tasty treat for tomorrow”, did she know what I meant and think “Tomorrow! I want it now”. I assume she had the capacity to understand the concept of the future as she would hide things (from the sneaky cat) for later retrieval, but I don’t think this would stand up to scientific scrutiny. I’m also puzzled by natural selection. I don’t question evolution; I just don’t get some aspects of it. I’m OK with the giraffes and long necks part, it’s what came before that which puzzles me, especially the part about the development of internal organs and systems. For us to stay alive all of our organs and their systems need to be operational. If the heart, or kidneys, or lungs fail us, the end point is exactly the same – death of the organism. Does this also mean that over the course of evolution these different systems developed in parallel, since the absence of any one of these could lead to the organism never being born or hatched? Maybe, there had been only a few organs that had multiple functions, which then became more specialized as subsystems developed and gained their (partial) independence.

We don’t have to go this far back to realize how complex biological processes can be. If all our cells start off the same, how is it that some of them become lymphocytes or neurons or kidney cells, and then behave accordingly? Then again, why do some of these cells get really messed up, becoming cancer cells that seem to feel that they can go anywhere they like and create a new colony (metastasis)? Furthermore, when we look into the machinery present within single cells of our bodies and brain, and examine how cells came to be able to communicate with one another, we need to wonder whether something so complex could have really evolved through natural selection, which necessarily involved trial and error until things were, to quote Goldilocks, ‘just right’. Then again, what are the alternatives?

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I suppose, aliens could have seeded the planet with all sorts of stuff that would come to make all the animals, so that they would evolve, two by two. God could have created the heavens and earth and all the lowly critters, then got bored and went off to create more exciting galaxies and worlds, leaving us to our own devices. Physicists might know the answers to these questions, especially as some of them are proposing the existence of multiple universes occupying the same physical space, and even that we can exist on several planes concurrently. Their talk about multi-universes frustrates me enormously, given that I can’t even understand much about the one I’m apparently in, although ‘the me’ that might be present in another universe might have better insights on this.

MULTIPLE CONVERGING SYSTEMS

Our ability to do all the things that we do is dependent on multiple processes all interacting with one another in precisely the right way at precisely the right time. Our brain holds sway on other systems which reciprocally affect brain functioning. This multidirectional communication requires considerable coordination within and between multiple systems. To an extent, this involves the influence of genetic factors that lay down the working drawings for these systems, which can be modified by experiences and environmental factors. This chapter provides a surface appreciation of:

- genetic processes that might contribute to the organization and functioning of systems that govern our functioning
- how the brain and its neuronal connections operate to affect various aspects of behavior and functioning of other body systems
- the contribution of growth factors (neurotrophic factors) to the formation and strengthening of new neuronal connections and the elaboration of neural circuits (neuroplasticity)
- the contribution of our endocrine systems to assure that metabolic processes are working as they should and what happens when they fail to do so
- how our immune system protects us from foreign particles that seem intent on harming us
- the involvement of gut bacteria, our microbiota, in determining our health and well-being.

A GENETICS PRIMER

A glance at Mendelian inheritance

Before getting into neurobiological systems, we’ll first consider genetic processes that govern their functioning. You’ll probably recall that your physical, biological, and behavioral characteristics (phenotypes) are determined, to an extent, by the genes you inherited from your parents (genotype).
One allele, or gene component, was inherited from your dad and one from your mom, and these could appear as either dominant or recessive. If you carried a dominant allele it alone would determine your phenotype, regardless of whether the other allele was dominant or recessive. The recessive phenotype would only appear if both alleles were recessive. Let’s imagine for a moment that hair color was determined by a single gene just as the color of pea plants (yellow versus green) might be. If your parents carried only the dominant gene for dark hair they would have this hair color, and so would you because you inherited only the genes for dark hair. Likewise, if both your parents carried the recessive allele, then you would have inherited only recessive alleles. If both your parents were heterozygous, carrying both a dominant and recessive allele, they would still be dark haired as the dominant gene for this trait was present. However, as you would inherit one allele from each of your parents, you could potentially inherit the recessive allele from each of your parents, and thus your hair color would differ from that of either of your parents. That example might be fine for pea plants and for simple phenotypes, but a given gene might not be fully dominant, and thus even if you carry the dominant gene, you might not fully resemble the dominant phenotype. As we’ll see repeatedly, as well, complex behaviors and complex illnesses don’t involve single genes, but instead involve the additive or interactive effects of many genes (polygenic effects). It also appears that the influence of genes can be moderated by environmental events. For that matter, environmental factors can alter the expression of genes themselves. Obviously, there’s more to inheritance than the brief description offered here, and many good texts are available to explain this further (e.g., Carey, 2003).

SCIENCE MAGIC

In the olden days, back when I was a kid in high school, it was understood that genotype influenced phenotype, but it was less clear how this actually came about. Particular genes were inherited and, seemingly through magic, particular traits and vulnerabilities somehow emerged. Most people never gave a thought to the processes by which this came about, even less than they considered how signals came through wires to create pictures on a TV screen. However, for those in fields related to health and well-being, including behavioral sciences, it is useful to understand at least some of the processes by which genes come to have the effects that they do, and to appreciate how the environment can, in some instances, dictate the actions of these genes.

The 23 pairs of chromosomes in humans each comprise coiled DNA made up of a very large number of small particles (varying from 100,000 to 3.75 million) referred to as nucleotides. These nucleotides are guanine (G), adenine (A), cytosine (C), and thymine (T), and the sequence of these bases provides the information that makes us what we are. Much as letters in the alphabet when strung together form words, in sets of three these nucleotides form amino acids, a series of which make up genes and regulatory elements of these genes that determine protein synthesis. Figure 3.1 provides a brief description of the flow of this process.

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More than 99% of our genome is common across all people, thus accounting for our many similarities. Certain genes, comprising about 1% of DNA, contain the information that contributes to the formation of all of our phenotypes, but a sequence of amino acids, referred to as promoter or regulatory region, tells the primary gene when to turn on or off, or even when to interact with other genes. As well, these regulatory processes can be affected by environmental events, such as stressors or toxins, so that the genes’ influence on neurobiological processes, such as hormone production, can be altered. In effect, contrary to the old view that the effects of genes
are more or less fixed, features of the environment may influence what these genes will actually do (Rands et al., 2014). A large portion of DNA carries what is referred to as junk DNA because it has no known function, although this doesn’t exclude the possibility that some functions will be discovered.

**GENE × ENVIRONMENT INTERACTIONS**

It had been thought at one time that for better or worse, whatever genes an individual inherited was what they were stuck with. This was hardly questioned and the great debates seemed to revolve around how much of a given phenotype was determined by genes and how much was the product of environment. Indeed, our phenotypic variance ($P_v$) was thought to reflect a combination of the variance contributed by our genes ($G_v$) plus our environment ($E_v$) plus the variance attributable to the gene × environment interaction. Although that sounds fairly reasonable, it turned out to be far too simplistic, since the expression of a gene can be influenced by the environment in which an organism is raised or tested. Studies of inbred strains of mice, in which every mouse of a given strain is identical to every other mouse (essentially being identical twins), have indicated that although they generally share behavioral phenotypes, even small environmental differences (e.g., where animals are bred) can create a marked divergence in the behavioral profiles that are evident (Crabbe et al., 1999). Furthermore, as we’ll see shortly, the environment can actually cause a change of gene functioning itself.

**Twin research methodology**

One approach to evaluate the extent to which a trait is genetically inherited is through twin studies. Monozygotic (identical) twins share all of their genes, whereas dizygotic (non-identical; fraternal) twins share only half their genes, and so one would expect that if a phenotype were primarily determined by genes, the phenotypic correlation between monozygotic twin pairs would be greater than among dizygotic twins. However, this relationship could also be affected by how twins were raised, particularly as monozygotic twins are often treated alike to a greater extent than are dizygotic twins, perhaps because they look alike and are, in a sense, interchangeable (Joseph, 2003). To dissociate the contribution of genes and environment to behavioral phenotypes, studies were conducted comparing phenotypes of identical twins that had been raised together versus those twins that had been raised apart (e.g., Elder et al., 2012). As useful as this paradigm might be, the conclusions that could be drawn were limited by a number of factors. Foremost in this regard is that the environment of twins reared apart is not actually entirely non-identical. It wasn’t as if one twin went into a good and the other into a modestly poor environment. In the main, twins end up in fairly similar middle- or upper-class homes. Furthermore, identical twins that had been raised apart had shared an intrauterine environment, and thus might have experienced a more similar prenatal environment than did fraternal twins.

Twin studies have been used to assess heritability in relation to many phenotypes (i.e., the extent to which a given characteristic or trait in a population is attributable to genetic differences). These have included physical pathologies, such as heart disease, various types of cancer, diabetes, addiction (alcohol, smoking), and just about any other physical and psychological disorder that
can be thought of. As well, studies have explored heritability in relation to social attitudes (e.g., socialism, abortion, gay rights, racial segregation), as well as dispositional and ideological orientations (neuroticism, agreeableness, religious fundamentalism, right-wing authoritarianism). Despite the many studies conducted to identify genetic contributions to personality factors on the basis of twin studies, in the main there has only been limited agreement concerning the contribution of genetic factors in this regard (Balestri et al., 2014). With advances in molecular genetics, particularly the ability to identify particular genes and gene mutations, twin studies have to a considerable extent been supplanted by alternative approaches tying specific genes to particular phenotypes.

**Gene polymorphisms**

The 20,000 or so genes that we carry are made up of approximately 3 billion nucleotide bases, and the precise sequence of these nucleotides are the same in each of the 10 trillion cells that are formed over the average life span. The transcription of DNA to mRNA is fairly complex, and almost every cell in a given individual ought to have an identical sequence of bases. In fact, nature has seen fit to include a proofreading process to limit the occurrence of errors (mutations), but with so much going on it is understandable that some errors will occur (Bertram, 2000). Some of these mutations (permanent changes of the sequence of nucleotides that comprise a gene) can be fairly extensive, as in the case of large deletions, amplifications (in which sections of the gene are duplicated), or translocations (the movement of a gene fragment from one location to another chromosome), or they can appear fairly innocuous, amounting to a change of a single nucleotide. A mutation, or a change of the gene sequence, that appears in a significant portion of the population (more than 1%) is referred to as a polymorphism, and those that involve only a single nucleotide are referred to as single nucleotide polymorphisms (SNP; pronounced snip). Mutations might occur owing to environmental influences (acquired mutations), such as ultraviolet radiation from the sun, or the presence of other toxic elements. Should these mutations occur within sperm or egg, they can be transmitted to the next generation (inherited mutations).

Change of a single nucleotide might not sound as if it’s very serious, and indeed it isn’t if this ‘mutation’ occurs on an unimportant portion of a DNA strand. But, if it occurs at some important portion of the gene, then changing just one nucleotide, just like changing one letter or word of a sentence can alter its entire meaning, the function of the gene can be entirely altered. For instance, a change of a single nucleotide or amino acid may alter the functional effects of the gene so that certain proteins (e.g., hormones or hormone receptors) may not form as they should.

One approach to link specific genes and phenotypes has made use of the ability to identify the presence of particular SNPs. Specifically, attempts have been made to determine whether individuals with or without a particular SNP display different phenotypes. However, given the vast number of cells formed, and the complexity of each DNA strand, it shouldn’t be surprising that a large number of mutations may occur, and several SNPs may even be present in a single gene. The frequency of SNPs varies with the length of the chromosome, numbering within the tens of thousands on each, reaching as high as 100,000 on some chromosomes. By virtue of the sheer number of SNPs that each of us carry, it is exceedingly difficult to link specific polymorphisms to particular phenotypes, especially as complex behaviors likely involve multiple
genetic contributions. Still, this approach has afforded researchers the opportunity to do this, although this involves using a very large cohort. However, some of the early studies linking SNPs to psychopathology weren’t replicated readily, possibly because of biases inherent in studies that involved a small number of participants.

The complexity of linking particular SNPs to phenotypic outcomes is compounded by several factors. The appearance of a given SNP may vary across cultures or societies. By example, a mutation on the gene for a particular hormone receptor (oxytocin) might appear at a rate of about 20% among Euro-Caucasians, but within Asian populations it is far more frequent, reaching 70–80% (Kim et al., 2011), and the influence of a SNP in one cultural group may differ from those involved in a second cultural group. Also, as we’ll see, a given SNP might interact with other genetic variations as well as with environmental or experiential factors (e.g., Caspi et al., 2003). Essentially, the presence of a particular genetic factor may represent a component, a vulnerability factor in a sense, but a particular outcome might not appear until a second hit, such as a stressor or toxicant, was encountered. This sort of interaction is not uncommon, and a two-hit hypothesis of this nature has been proposed in relation to depressive disorders, certain types of cancer, Parkinson’s disease, and stroke recovery (e.g., Carvey et al., 2006; Caspi et al., 2003).

### MUTATIONS IN HOSTILE ENVIRONMENTS

The term ‘mutation’ brings up the thought of some creature like the Hulk or Ninja Turtle, or something that’s quite negative. Yet, mutations may well be an essential component of evolution and may have actually been responsible for making us as fit as we are. When bacteria, such as Escherichia coli (E. coli), were exposed to a challenging environment that comprised either potential starvation or the presence of an antibacterial agent (antibiotic) that could kill them, the rate of mutation (mutagenesis) in the E. coli genes increased appreciably (bacteria, like other organisms, carry genes). In essence, features of the bacterial genes might have changed in an effort to adapt to the relatively hostile conditions present (Amar et al., 2012). Ordinarily, when an antibiotic was present, most bacteria would be destroyed. However, if there were a great number of different bacteria present (bacterial diversity), or if there were bacteria that had mutated so that they could survive the antibacterial onslaught, they might have contributed to the formation of new bacterial colonies carrying the mutation and would be more resistant should the antibiotic again be present. Thus, mutations can serve as a survival mechanism for the bacterial species, and the more mutations that occur, the greater the likelihood of species survival. Mutations could similarly proliferate in humans with increasingly more hostile environments, and those that enhanced fitness would be most likely to be preserved within the gene pool and passed down across generations (Nei, 2013). In essence, challenges favor the preservation of certain mutations, which is a fundamental driving force for evolution.
Epigenetics

There are several common misconceptions regarding the influence of genes on behavior. How often do we hear the notion that a person inherited particular genes and thus they necessarily will express some sort of phenotype? To an extent this is accurate, but genes often don’t act alone, nor are the phenotypic effects of genes immutable. While some genes contain the information for the formation of a phenotype, as described earlier, the nearby gene promoter region tells the primary gene when it ought to turn on or off, and whether a gene should be interacting with other genes. Thus, some genes serve to define a phenotype, whereas aspects of a promoter gene act as the instruction manual that guides the gene’s action. If the actions of these promoter genes change, which can occur through the influence of the environment or experiences, then the actions of genes that give rise to a particular phenotype can be altered.

The notion that both genes and environment contribute to phenotypes is hardly new, but what hadn’t been expected was that experiential and environmental factors would actually influence how genes were expressed. Specifically, it seems that under some conditions (e.g., in response to stressors, the presence of particular toxicants, or even some foods), epigenetic changes may occur in which the actions of some genes or their promoters may be suppressed, but without altering the DNA sequence (Bird, 2007; Szyf et al., 2005). In effect, the gene itself was unaltered, but its functioning was turned off.

Epigenetic changes may come to influence many biological processes (hormones and hormone receptors, growth factors, immune elements) and might thereby contribute to a variety of psychological disorders, such as depression, PTSD, and addiction (Maze et al., 2010; Mehta et al., 2013) as well as physical disease states, such as many forms of cancer, heart disease, and autoimmune disorders. Given that epigenetic changes, like mutations discussed earlier, can instigate disease processes, there have been efforts to fight illnesses, such as cancer, through drug treatments that could reverse (reprogram) these destructive epigenetically-derived disturbances. However, as this could end up having negative consequences on non-cancerous cells, targeting these treatments appropriately may turn out to be difficult. Furthermore, there may be a large number of epigenetic changes associated with a given pathology (Labonté et al., 2013), making it difficult to identify which are causally linked to outcomes, which are provoked by the pathology, and which might simply be bystanders. The presence of epigenetic marks that occur in concert with pathology, even if they are not causally involved in the illness, may nevertheless be significant as they could serve as biomarkers to predict the occurrence of later pathology (Kundakovic et al., 2015).

Epigenetics and intergeneration actions

Epigenetic effects are not only significant because of their effects on gene expression and disease processes, but also because they can occur owing to events that occurred prenatally and early in development (Szyf et al., 2005) and can persist over the course of an organism’s life, giving rise to later behavioral or physical changes (Essex et al., 2013). Moreover, if the epigenetic changes occur within germ line cells (egg or sperm), then they can be transmitted from one generation to the next. In effect, biological and behavioral effects elicited in a given individual as a result
of environmental triggers (psychosocial factors or what mom eats) can be recapitulated in their children and grandchildren (Franklin et al., 2010; Lillycrop, 2011). Pesticides, such as methoxychlor (which, ironically, was a replacement for the highly dangerous pesticide DDT until it was banned in the US in 2003 because of its actions on hormone systems), which has known epigenetic actions, can have effects that appear over several generations (Manikkam et al., 2014). As such, the increase of diseases we are seeing today could actually be due to events experienced by our forebears.

As negative experiences, such as social strife and poverty, can profoundly influence the course of development and can serve to increase vulnerability to pathology, it has been said that “society itself should be considered ‘an environment’ that through epigenetic actions can affect cognitive, emotional, and physical health” (Branscombe & Reynolds, 2015: 10). It is particularly significant that despite the persistence of epigenetic changes, they are modifiable so that even if a gene is silenced, this can be reversed. Such changes have been achieved through drug interventions, but can perhaps emerge through positive nurturing (Weaver et al., 2005).

THE NERVOUS SYSTEM

Through networks of billions of neurons that are able to talk to one another in a highly coordinated manner, our central nervous system (CNS), which comprises the brain and spinal cord, is fundamental for sensory processes, motor outputs, cognitive functioning, memory, emotions, as well as processes associated with primitive drives (eating, thirst, sex, sleep) and energy regulation. In addition, the brain also influences its cousin, the peripheral nervous system, including autonomic activity that controls involuntary functioning (e.g., heart activity, digestion), and profoundly influences immune and hormonal processes.

Neuronal system

Our many neurons have thousands of branches, which have their own smaller branches coming off of them, and each of these has many, many synapses. With all this wiring running all over the place, one would think it would be a hodge-podge of circuits, held together by some neuronal duct tape. However, brain wiring is actually highly organized, with large and small tracts going off to different places in a predetermined, genetically encoded manner. For the sake of simplicity, we’re often told that various brain regions serve different functions. To a considerable extent this is correct, but in dealing with complex behaviors or pathological conditions, we can pretty well be assured that these are determined by neuronal systems that involve several brain regions operating sequentially or in parallel. For example, a syndrome such as post-traumatic stress disorder (PTSD) may involve brain regions governing fear (aspects of the amygdala), memory of the trauma (hippocampus), and judgment and appraisals (aspects of the prefrontal cortex). Likewise, addictions may involve areas associated with anxiety (aspects of the amygdala), cognitive processes and impulsivity (prefrontal cortex), and reward processes (nucleus accumbens) (e.g., Kalivas & Volkow, 2011). Indeed, even seemingly basic functions, such as eating or sex, are influenced by systems involving interconnections between multiple brain regions.
Figure 3.2 Depiction of a neuron. Each of the many billions of neurons in the brain has a primary, lengthy tentacle, termed an axon coming from its cell body (soma), which is essential for transmitting information to other cells (see Figure 3.2). A neuron also has many smaller tentacles coming from it, referred to as dendrites, which are responsible for receiving information. Minute electrical stimuli can be generated within an axon, so that where it meets the dendrites of an adjacent postsynaptic neuron (referred to as a synapse), the electrical pulse will cause a chemical (neurotransmitter) to be released from the axon terminals that will stimulate receptors present on the dendrites or cell body of this next neuron. In the main, each neuron contains one type of chemical (although more than one can occur in some instances), but because many receptors are present, each of which can be stimulated by a different neurotransmitter, messages can be received from a great number of different types of neurons.

Brain cells and how they function: Neurotransmission

Neuronal functioning involves a large number of neurotransmitters, including norepinephrine, dopamine, serotonin, acetylcholine, GABA, glutamate, as well as neuropeptides such as β-endorphin, dynorphin, and encephalin. To this point, more than 100 neurotransmitters (or potential neurotransmitters) have been discovered, and for many of these several different receptors have been identified. Neurotransmitters can have different functional effects across brain regions, and the presence of these receptors, like the neurotransmitters themselves, can either decrease or increase, depending on conditions experienced. Obviously, with such a great array of neurotransmitters and receptors, and so many neurons in play at any given time, considerable coordination is needed. To this end, in addition to neurotransmitters that excite the activity of other neurons, in order to diminish sources of noise and to regulate the degree of neuronal activity transmitters are present, such as GABA, that act in an inhibitory capacity, essentially causing certain cells to be quiet while others are active (Anisman et al., 2008).

The various neurotransmitters and their receptors across brain regions serve in different ways. Within limbic brain regions (e.g., hippocampus, amygdala, and prefrontal cortex) they may be
associated with emotions, executive functioning (appraisals, decision making), and memory processes, whereas in hypothalamic nuclei (e.g., paraventricular nucleus, arcuate nucleus) they interact with several hormones to affect basic functioning, such as energy regulation, feeding, and sexual behavior. A given neurotransmitter may have multiple functions, depending upon the brain region involved. By example, dopamine activation within the ventral tegmentum and the nucleus accumbens is associated with reward processes, and excessive activity of particular dopamine receptors in cortical regions is accompanied by schizophrenia, whereas a loss of dopamine within another brain region, the substantia nigra, is associated with Parkinson’s disease. It similarly appears that the action of norepinephrine at the locus coeruleus is involved in vigilance, in the amygdala it can be associated with fear memories, and at the hypothalamus it may serve in the regulation of autonomic functioning. Thus, in describing the action of these and each of the other transmitters we’ll discuss, it’s essential to distinguish between the brain regions in which they are acting. In fact, there are occasions in which a drug is administered to reverse particular neurological disturbances by stimulating a neurotransmitter in one region, only to have other disturbed behaviors emerge because the drug also affects brain regions that hadn’t been impaired at the outset. For instance, administration of a drug to increase dopamine to attenuate symptoms of Parkinson’s disease may promote gambling addiction because the drug also affects reward processes related to dopamine functioning within the nucleus accumbens.

Receptor functions

When a neurotransmitter is released from vesicles present at the terminal region of an axon, it travels across the synaptic cleft to stimulate receptors that are present on an adjacent neuron (postsynaptic neuron), which causes its activation. For most neurotransmitters and hormones there may be several types of receptors present and when stimulated they may each have different effects on a variety of outcome measures. In addition to the receptors present on the adjacent neuron, located at the presynaptic end of each axon are receptors, termed autoreceptors, which, upon being stimulated by the neurotransmitter that has been released, have the effect of telling the neuron to slow down the production of the neurotransmitter. Thus, as the amount of neurotransmitter released into the synapse increases, these autoreceptors are more likely to be triggered, and, through this feedback process, the neurotransmitter production is self-regulated. In addition to being affected by these endogenous factors (those ordinarily present within the body or brain), an increase or decrease of neurotransmitter functioning can be accomplished through exogenous administration (introduced from an external source) of drugs that either stimulate or block receptors. Agents that directly stimulate receptors, essentially acting much like the neurotransmitter, are termed agonists, whereas those that bind to the receptor and prevent stimulation from occurring are referred to as antagonists.

Turnover and reuptake

In considering the relationship between neurotransmitter functioning and the emergence of pathology, it’s not sufficient to simply know how much of a particular transmitter is present, but also how much neurotransmitter is actually produced and released (turnover), which specific receptors are being triggered, how they might affect and be affected by specific hormones or other neurotransmitters, and where in the brain these changes are occurring.
Having been released from storage vesicles at the terminals of axons and stimulated postsynaptic receptors, the neurotransmitter needs to be eliminated. Some of the transmitter is degraded by enzymes present in the synaptic cleft, but in the case of many transmitters it can also be transported back into the cell (by a transporter mechanism) through a process called reuptake, thereby making it available for later reuse (our own little environmentally-friendly recycling plant). The longer the neurotransmitter stays in the synaptic cleft, the greater the chances are that a receptor will be stimulated. Accordingly, the efficiency of the neurotransmitter can be increased by pharmacologically increasing its time in the synaptic cleft. This can be achieved by inhibiting enzymes that ordinarily destroy the transmitter or, alternatively, by inhibiting the reuptake of the transmitter back into the neuron. The latter process is how drugs, such as the selective serotonin reuptake inhibitors (SSRIs) used in the treatment of depression, might have their effects (Zhou et al., 2007), although there’s a good chance that the antidepressant actions might come from other actions of these agents.

NEUROLOGICAL VERSUS MENTAL DISORDERS

The boundaries between a disorder and what constitutes a mental disorder are vague. In general, though, neurological disorders comprise those that involve structural, biochemical, or electrical abnormalities in the brain, spinal cord, or other nerves, which promote varied symptoms (depending on the brain region involved), such as altered levels of consciousness, confusion, paralysis, seizures, poor coordination, muscle weakness, pain, and loss of sensation. Relatively common neurological disturbances include Alzheimer’s disease, Parkinson’s disease, epilepsy, amyotrophic lateral sclerosis (ALS), stroke, brain tumors, migraine (and other headache disorders), multiple sclerosis, neuroinflammation, trauma to the nervous system, neurological disorders that occur as a result of malnutrition, conditions that involve sensory, motor, or learning disabilities (e.g., agnosia, aphasia, ataxia, apraxia), as well as childhood conditions such as autism and attention deficit hyperactivity disorder (ADHD). These are only a portion of the long list of neurological disorders provided by the National Institute of Neurological Disorders and Stroke.

Mental disorders are more commonly considered to be those that involve changes of how a person feels, thinks, perceives, or acts, often varying with the social context. Unlike some neurological disorders, which typically involve gross neuronal damage, mental disorders might not be accompanied by such frank damage, and more often involve disturbances of neuronal activity. Thus, mental disorders might not always be as readily diagnosed, and often are determined on the basis of behavioral analyses rather than discrete physical characteristics. A wide variety of mental disorders exist, ranging from disturbances of mood and anxiety, personality, sleep, eating, and sexual behaviors, as well as developmental and conduct disorders. Most often, these conditions are treated through behavioral therapies or drug treatments, although other options, such as transmagnetic
brain stimulation, electroconvulsive stimulation, and surgical procedures (e.g., deep brain stimulation through electrical pulses to specific brain regions), have been used.

Psychiatric and neurological impairments both involve and can be influenced by neuronal disturbances, as well as psychological and social processes. More than this, traumatic brain injury can give rise to fear and anxiety associated with PTSD, just as it may be a risk factor for dementia (Gardner et al., 2014). Moreover, disorders such as PTSD, schizophrenia, depressive disorders, bipolar disorder, and obsessive compulsive disorder are all accompanied by structural brain changes, including the diminished size of several brain regions (White et al., 2012). Despite their overlapping features, psychiatric and neurological disorders have lived and been treated in different silos, but there have been repeated calls for better integration between these fields (Insel et al., 2010).

Glial cells

The brain’s second type of cell, known as glial cells, had at one time not been a focus of great interest, only receiving occasional lip service. These cells were thought to be ‘the help’, serving as support cells, providing nutrients and taking away debris, and hence weren’t considered as being directly related to cognitive processes. However, it became apparent that glial cells do much more, being fundamental in the clearance of neurotransmitters from the synaptic cleft, thereby preventing damaging effects attributable to a build-up of some transmitters, such as glutamate. As well, within some brain regions they can act like neurons in the transmission of information (Newman, 2003).

Several types of glial cells have been identified that serve in different capacities. Oligodendrocytes are involved in the myelination of neurons (myelin forms a sheath around axons) that allows for the rapid propagation of electrical signals down the axon (in the periphery, Schwann cells serve in this capacity). Astrocytes, the most abundant type of glial cell, are involved in maintaining ion balances within fluid outside brain cells, and play a fundamental role in the repair of brain and spinal cord neurons. They are also smarter than we thought, and are able to communicate with neurons by the release of particular neurotransmitters (e.g., GABA, glutamate) (Allen & Barres, 2005). More than this, astrocytes have another exceedingly important function. Specifically, they begin to form neurons in areas of the brain damaged by stroke, and in this way may be important for repair of brain damage (Kokaia & Lindvall, 2012; Magnusson et al., 2014).

Still another type of glial cell, microglia, are constantly in search of potentially damaging factors, such as plaque and infectious agents, and they typically eliminate those that pose a risk to neurons (Rivest, 2009). Although their role is meant to be one of protecting the brain through the release of chemicals that trigger inflammation (as we’ll see later in this chapter, inflammation may reflect an adaptive response), microglia can also have some very negative effects (Ekdahl et al., 2009). Specifically, if the inflammatory response elicited by microglia becomes too great, neurodestructive actions may ensue, thereby promoting neurodegenerative disorders, such as Alzheimer’s and Parkinson’s disease, as well as mood-related disorders (Litteljohn & Hayley, 2012).
AUTONOMIC NERVOUS SYSTEM

Sympathetic and parasympathetic activity

The autonomic nervous system (ANS) is the portion of our nervous system which regulates body organs and processes over which we don’t have voluntary control (e.g., heart, gut, stomach). The primary brain region involved in the regulation of the ANS is the medulla oblongata. Other brain regions involved in regulating the ANS include the hypothalamus, which is involved in eating and drinking, and the amygdala, which is related to emotional responses.

The ANS comprises two subsystems, the sympathetic nervous system (involving the release of epinephrine, also referred to as adrenaline), which is responsible for activating various organs (e.g., stimulating the sympathetic system will increase the heart rate), and the parasympathetic system (involving the release of acetylcholine), which acts against the actions of the sympathetic system (e.g., Brodal, 2004). These complementary systems ordinarily are in balance with one another, but occasionally environmental triggers will instigate changes so that sympathetic activity predominates, as observed in response to emotionally arousing events that produce an increase of blood pressure and heart rate. In other instances the compensatory antagonistic system may be overly active, and thus blood pressure and heart rate may become inordinately low.

ENDOCRINE SYSTEMS

Hormones share several characteristics with neurotransmitters, serving as chemical signaling molecules that are released by a cell or by a gland in response to external or internal signals (e.g., changes of glucose levels or in response to stressors). Whereas neurotransmitters travel very short distances to excite receptors on adjacent neurons, hormones can enter the bloodstream and then travel to distal sites where they trigger specific receptors present on cells. Some hormones, referred to as endocrine hormones, are released directly into the bloodstream, whereas exocrine hormones are secreted directly into a duct and then flow either into the bloodstream or spread from cell to cell by diffusion. Furthermore, several hormone-like substances are manufactured within the brain and can act as if they were neurotransmitters that activate particular types of receptors. These receptor types are present in differing concentrations across brain regions, and may have very diverse functions or even opposing actions.

Hormones and what they do

Hormones are manufactured and released from different sites (as described in Tables 3.1–3.4), and have different functions. They may be involved in the operation of metabolic processes, cell growth and cell death (apoptosis), stress reactions, eating and energy balances, sexual characteristics and behaviors, and they can influence brain functioning. Moreover, dysfunction of hormone systems can lead to various illnesses and might contribute to the sex differences that have been related to illnesses, such as heart disease and autoimmune disorders (Lleo et al., 2008).
HORMONES ASSOCIATED WITH THE STRESS RESPONSE

As stressful events affect various psychological and physical disorders, considerable attention has been devoted to the involvement of stress-related hormones in these pathological conditions. Once again, these hormones don’t act in isolation of other processes, and can interact with other hormones or with brain neurotransmitter systems in determining behavioral and physical well-being and illnesses. Thus, even though we often consider the role of hormones in relation to various conditions, the potential cross-talk between diverse systems should be kept in mind.

HPA responses

Among the most examined stress systems are those related to autonomic nervous system functioning (e.g., epinephrine and norepinephrine), and those of the hypothalamic-pituitary-adrenal (HPA) system (see Table 3.1). We’ll cover this in greater detail in Chapter 5, but for the moment, it is suffice to say that stressors cause activation of brain processes that instigate the release of corticotropin releasing hormone (CRH) from the hypothalamus, which stimulates the secretion of adrenocorticotropic hormone (ACTH) from the pituitary gland that lies at the base of the brain. The ACTH enters the bloodstream and upon reaching the adrenal gland it stimulates the release of cortisol (in rodents, corticosterone, rather than cortisol, is released). Activation of this system facilitates our ability to deal with challenges but, in some instances, problems might arise, especially when hormone release is excessive and occurs over a protracted period, ultimately promoting pathological outcomes, including neurodegenerative disorders. It is important to underscore that these are only some of the many hormones altered by stressors. Moreover, virtually every hormone affected by stressors is also affected by other variables, including those related to eating and energy regulating processes, and indeed, these hormones are all known to have multiple actions.

Table 3.1  Hormones related to stress responses

<table>
<thead>
<tr>
<th>Secreted hormone</th>
<th>Biological effect</th>
<th>Behavioral outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticotropin-releasing hormone (CRH)</td>
<td>Formed in the paraventricular nucleus of the hypothalamus, as well as several limbic and cortical regions. Stimulates ACTH release from the pituitary gland.</td>
<td>Involved in stress responses, promoting fear and anxiety, and contributes to eating processes. In addition to being fundamental to stress responses, it diminishes food intake and increases metabolic rate.</td>
</tr>
<tr>
<td>Adrenocorticotropic hormone (ACTH)</td>
<td>Formed in the anterior pituitary gland. Stimulates corticosteroid (glucocorticoid and mineralocorticoid) release from adrenocortical cells.</td>
<td>Stress responses elicited are primarily due to actions on adrenal corticoids.</td>
</tr>
</tbody>
</table>

(Continued)
Table 3.1  (Continued)

<table>
<thead>
<tr>
<th>Secreted hormone</th>
<th>Biological effect</th>
<th>Behavioral outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arginine vasopressin (AVP)</td>
<td>Released by both the paraventricular and supraoptic nucleus: promotes water reabsorption and increased blood ACTH.</td>
<td>Together with CRH, may synergistically increase stress responses. Influences social behaviors.</td>
</tr>
<tr>
<td>Cortisol (corticosterone in rodents)</td>
<td>Released from the adrenal gland. Has anti-inflammatory effect, promotes release and utilization of glucose stores from liver and muscle, and increases fat storage.</td>
<td>Prototypical stress hormone; influences defensive behaviors, affects memory processes, stimulates caloric intake, and may promote preference for high calorie foods under stressful circumstances (stimulates consumption of comfort foods).</td>
</tr>
<tr>
<td>Mineralocorticoids (e.g., aldosterone)</td>
<td>Released from the adrenal gland. Stimulate active sodium reabsorption and passive water reabsorption, thus increasing blood volume and blood pressure.</td>
<td>Increased aldosterone influences salt and water balance. Excessive sodium and water retention leads to hypertension. Low levels of aldosterone leads to a salt-wasting condition evident in Addison’s disease.</td>
</tr>
<tr>
<td>Epinephrine (EPI) (adrenaline) and norepinephrine (NE) (noradrenaline)</td>
<td>Produced in the adrenal gland (medulla) and within sympathetic neurons; increases oxygen and glucose to the brain and muscles; promotes vasodilation; increases catalysis of glycogen in liver and the breakdown of lipids in fat cells; increases respiration and blood pressure; suppresses bodily processes (e.g., digestion) during emergency responses; influences immune system activity.</td>
<td>Elicits fight or flight response. In the brain, EPI and NE have multiple behavioral actions related to defensive behaviors (e.g., vigilance, attention).</td>
</tr>
<tr>
<td>Beta-endorphin</td>
<td>Secreted from several sites, such as the arcuate nucleus.</td>
<td>Inhibits perception of pain.</td>
</tr>
</tbody>
</table>

EATING AND ENERGY-RELATED HORMONES

Several hormones play a fundamental role in energy regulation processes and balances, being involved in either the initiation of eating or its cessation. These same hormones are also integrally involved in stress responses and may contribute to stress-related psychological disorders. Many of these hormones are referred to in Table 3.2. In addition, there are several other hormones that are associated with metabolic responses (storage or use of nutrients), including growth hormone, prolactin, and thyroid hormones.
### Table 3.2  Hormones related to energy regulation and eating

<table>
<thead>
<tr>
<th>Secreted hormone</th>
<th>Biological effect</th>
<th>Behavioral outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptin</td>
<td>Produced by fat cells. Influences neurons in hypothalamic regions.</td>
<td>Reduces food intake and appetite, and increases energy expenditure.</td>
</tr>
<tr>
<td>Ghrelin</td>
<td>Produced in gut. Affects same brain regions as leptin, but in an opposite manner.</td>
<td>Stimulates food intake and appetite, while reducing energy expenditure. Enhances reward-seeking behaviors; modulates stress responses.</td>
</tr>
<tr>
<td>Insulin</td>
<td>Produced by beta cells in the pancreas. Regulates fat and carbohydrate metabolism.</td>
<td>In brain, insulin stimulates hormones that reduce food intake.</td>
</tr>
<tr>
<td>Bombesin (appears in humans as neuromedin B [NMB] and gastrin releasing peptide [GRP])</td>
<td>Produced in gut and in several brain regions.</td>
<td>Acts as a satiety peptide (signals when individual is full) and is released in response to stress, thereby promoting anxiety.</td>
</tr>
<tr>
<td>Neuropeptide Y (NPY)</td>
<td>Produced by the gut and in several brain regions, including the hypothalamic arcuate nucleus. Increases vasoconstrictor actions of norepinephrine.</td>
<td>Increases food intake and reduces physical activity; increases energy stored in the form of fat; blocks nociceptive (noxious) signals to the brain; acts as an anxiolytic agent.</td>
</tr>
<tr>
<td>Orexin (hypocretin)</td>
<td>Produced within the lateral hypothalamus, but orexin receptors are found throughout the brain.</td>
<td>Involved in appetite, as well as stress and reward processes, arousal, and wakefulness.</td>
</tr>
<tr>
<td>α-Melanocyte stimulating hormone (α-MSH)</td>
<td>Produced in the arcuate nucleus of the hypothalamus. Acts as an agonist of melanocortin (MC-3 and MC-4) receptors in the brain, including stress-related regions.</td>
<td>Reduces appetite, increases energy expenditure as modulated by leptin.</td>
</tr>
<tr>
<td>Agouti-related peptide (AGRP)</td>
<td>Produced in the arcuate nucleus (by same cells that produce NPY), and serves as a natural antagonist of MC-3 and MC-4 receptors.</td>
<td>Increases appetite and reduces energy expenditure. Modulated by leptin and ghrelin.</td>
</tr>
</tbody>
</table>
Leptin
The discovery of the hormone leptin has been considered among the most important research findings in the field of energy balance. Produced primarily by adipocytes (fat cells), this hormone enters circulation and then, by affecting the brain and peripheral organs, reduces food intake, increasing energy expenditure and reducing adiposity (fat) (Zhang et al., 1994). Leptin also influences HPA axis activity, and promotes the release of neurotransmitters such as serotonin and dopamine, thereby inhibiting reward-seeking behaviors and affective tone related to feeding, and mood states (Abizaid et al., 2014; Fulton et al., 2006). Leptin isn’t alone in serving as a satiety signal (i.e., a stop signal), as other less studied hormones, such as neuromedin B (NMB) and gastrin-releasing peptide (GRP), also serve in this capacity, and they too have effects on emotional processes (Moody & Merali, 2004).

Ghrelin
Opposing the actions of leptin, elevated levels of ghrelin are associated with increased food consumption (Abizaid & Horvath, 2008). The levels of ghrelin increase just before meal-time, presumably signaling us to eat (or acting as a preparatory response for food we’re about to eat), and then declines after we’ve eaten. Dysfunction of ghrelin functioning is related to disturbed energy and feeding processes, in that elevated ghrelin occurs in anorexia and bulimia nervosa, whereas binge eating was associated with decreased ghrelin (Geliebter et al., 2005).

Like other eating-related peptides, ghrelin activates dopamine neurons that are involved in reward processes, and could thus be an intermediary step for the rewarding feelings derived from food (Abizaid, 2009). In fact, eating was increased by ghrelin injected directly into the ventral tegmental region of the brain, which is involved in reward processes, whereas ghrelin antagonists had the opposite effect. Ghrelin also directly stimulates orexin receptors in the lateral hypothalamus (orexin is a hormone that has been associated with food craving), as well as cells in several other hypothalamic nuclei. Furthermore, in humans, ghrelin administration increased food-related imagery and stimulated reward pathways, thus implicating ghrelin in appetitive responses to incentive cues (i.e., visual and olfactory cues that had been associated with reward) that promote food cravings (Schmid et al., 2005).

Insulin
The main job of insulin is to have cells in the body take up glucose from the blood, and then store it as glycogen. When insulin is absent or when the response to insulin is diminished, glucose won’t readily be taken up into cells, leading to diabetes. In addition, insulin interacts with cortisol, as well as leptin and other regulatory hormones that have been implicated in the development of obesity and metabolic disturbances associated with chronic stressors. Clearly, multiple processes play into eating behaviors; some stimulate hunger or satiety, or influence energy production and use, whereas others influence the rewarding value obtained from food and contribute to the cravings we feel for some of these.
SEX HORMONES

Estrogen and testosterone

Often referred to as gonadal steroids, sex hormones in males comprise androgens (primarily testosterone, as well as androstenedione, dehydroepiandrosterone, and dihydrotestosterone), and in females these consist of estrogens (primarily estradiol, and also estriol and estrone) as well as progesterones. As indicated in Table 3.3, testosterone is formed in the testis, and to a lesser extent in the adrenal glands. Estrogen is formed in the ovaries following stimulation by follicle-stimulating hormone (FSH), although smaller amounts of estrogen can also be formed by other tissues and by fat cells (Nelson & Bulun, 2001).

Table 3.3 Sex hormones

<table>
<thead>
<tr>
<th>Secreted hormone</th>
<th>Biological effect</th>
<th>Behavioral outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone</td>
<td>Male steroid hormone produced in the testis in males and ovaries in females. To a lesser extent is produced in adrenal glands. Involved in the development and sexual differentiation of brain and reproductive organs. Fundamental in secondary sexual features, including body hair, muscle, and bone mass.</td>
<td>Associated with sexual behavior and libido. Linked to aggressive and dominant behaviors.</td>
</tr>
<tr>
<td>Dehydroepiandrosterone (DHEA)</td>
<td>In males, produced in adrenals, gonads, and brain. Acts as an anabolic steroid to affect muscle development.</td>
<td>Acts like testosterone. Has been implicated in maintaining youth.</td>
</tr>
<tr>
<td>Estrogens (estrone, estradiol, estriol)</td>
<td>Estradiol is predominant of the 3 estrogens produced in the ovaries. Principle steroid regulating hypotalamic-pituitary ovarian axis functioning. Involved in protein synthesis, fluid balances, gastrointestinal functioning and coagulation, cholesterol levels and fat depositions. Affects bone density, liver, arterial blood flow, and has multiple functions in the brain.</td>
<td>Influences female reproductive processes and sexual development. Important for maternal behavior, maintaining cognition, as well as anxiety and stress responses.</td>
</tr>
<tr>
<td>Progesterone</td>
<td>Formed in the ovary; precursor for several hormones; involved in triggering menstruation, and for maintaining pregnancy (e.g., inhibits immune response directed at embryo); reduces uterine smooth muscle contraction; influences resilience of various tissues (bones, joints, tendons, ligaments, skin).</td>
<td>Influences female reproductive processes and sexual development. Affects maternal behavior, disturbs cognitive processes. Has anti-anxiety actions.</td>
</tr>
</tbody>
</table>
Luteinizing hormone (LH) is produced in the anterior pituitary gland. In females, an 'LH surge' triggers ovulation and development of the corpus luteum, an endocrine structure that develops from an ovarian follicle during the luteal phase of the estrous cycle. Behavioral changes associated with estrogen or testosterone are elicited indirectly through actions on other steroids.

Follicle stimulating hormone (FSH) is secreted from the anterior pituitary gland; it regulates development, growth, pubertal maturation, and reproductive processes. Together with LH, it acts synergistically in reproduction and ovulation. Behavioral changes associated with estrogen or testosterone are elicited indirectly through actions on other steroids.

Table 3.3 (Continued)

<table>
<thead>
<tr>
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</tr>
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<tbody>
<tr>
<td>Luteinizing hormone</td>
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<td>Behavioral changes associated with estrogen or testosterone are elicited indirectly</td>
</tr>
<tr>
<td>FSH</td>
<td>ovulation and development of the corpus luteum, an endocrine structure that</td>
<td>through actions on other steroids.</td>
</tr>
<tr>
<td></td>
<td>develops from an ovarian follicle during the luteal phase of the estrous cycle.</td>
<td></td>
</tr>
</tbody>
</table>

Estrogens are, of course, best known for their role in the development of female secondary sexual characteristics (e.g., breasts), in the regulation of the menstrual cycle, and a surge of estrogen promotes luteinizing hormone release, which triggers ovulation. Figure 3.3 shows some of the hormonal changes that occur over the menstrual cycle, depicting the relation to body temperature, lining of the uterus, menstruation, and ovulation. But, as indicated in Table 3.3, there’s much more to estrogen’s action than that. Estrogens are also involved in stimulating sexual receptivity, metabolic process, increasing fat stores, stimulation of endometrial growth (associated with menstruation), and enhancing uterine growth, and together with progesterone maintains the uterus lining for the implantation of a fertilized egg (Christensen et al., 2011). As well, estrogen enhances bone formation and reduces bone resorption, and bone weakness is often observed after menopause. Beyond these actions, estrogen also affects cardiac and lung functioning, and may influence hormone-dependent cancers (Rosano & Panina, 1999).

As the levels of sex hormones decline at menopause, and various negative symptoms begin to emerge (e.g., diminished bone density), hormone replacement therapies became popular in an effort to mitigate these outcomes. Particular attention was delivered to what were referred to as compounded ‘biodentical hormones’ that were said to have precisely the same chemical and molecular structure as hormones that are ‘naturally’ made in the body. The use of hormone therapy generally declined with reports that this form of treatment could have severe adverse effects. It seems, however, that hormone replacements are still being used, often in the form of the biodentical hormones that can be obtained through the internet or directly from suppliers, even though these compounds have not received approval from the Federal Drug Administration (FDA). In fact, many of the treatments purchased from these sources may not provide accurate amounts of hormone, may have serious health consequences, and many women using these compounded hormones are unaware of the health risks they’re placing on themselves (Pinkerton & Santoro, 2015).
Figure 3.3 Variations of hormones from the pituitary gland (follicle stimulating hormone (FSH) and luteinizing hormone (LH)) as well as estrogen and progesterone) over the menstrual cycle, together with changes of body temperature, uterine status, menstruation, and ovulation.

('What happens menstrual cycle hormone ovary basal body Uterus' www.pcosjournal.com)

The production of testosterone is influenced by hypothalamic and pituitary processes, and can be affected by psychological factors. Much like its female counterpart, testosterone is pivotal in the production of male reproductive organs (testis, prostate) as well as the development of
secondary male features, such as the growth of body hair, muscle growth, and bone density, and has been linked to dominance challenges and aggressive behaviors (Sapolsky, 2005; Sapolsky et al., 2000). Testosterone may have important implications for health, and low levels of this hormone have been associated with heart disease, just as they have been associated with mood changes; hormone replacement treatments have been used to counter these effects. Although testosterone is essential for male development, it is also formed in females, and when levels are too low, vulnerability to obesity increased, as did body fat and heart disease (Fagman et al., 2014).

**JUICING**

Most people, especially those who follow sports, might be aware that anabolic and androgenic steroids have been used by athletes to gain an advantage over their competitors, and even young people have been using these agents in an effort to get a head start. At high doses these steroids contribute to the development of muscles, and hence greater strength and enhanced athletic performance. It’s unfortunate for users that these steroids have a considerable down side, negatively influencing the heart and liver, creating immune system disturbances, and skin (complexion) problems. Moreover, steroids also affect brain neurotransmitters, thereby influencing emotional and cognitive functioning. As much as they can have negative consequences in adults, still more profound negative consequences can occur in adolescents, in whom frontal cortical functioning is still developing, which can obviously have long-term repercussions.

**Prolactin**

Although estrogens and androgens have received the greatest attention in relation to sex-related behaviors and development, other hormones also contribute in this regard. The prime function of prolactin, which is released from the anterior pituitary, is that of promoting lactation. Prolactin is stimulated by suckling in mammals, and among birds by tactile and visual stimuli from the nest, eggs, or chicks themselves. In addition to maternally-related behaviors, prolactin also contributes to several other essential biological processes, including sexual behavior and sexual pleasure, eating-related processes, pain perception, and responses to emotional stressors.

**‘BREAST IS BEST’**

Humans are the only species in which women can opt not to breast feed their infants and substitute this with formulas. Breast feeding occurs across countries and cultures, but tends to be more common in non-industrialized countries, possibly because of the costs of alternatives. In some countries...
paid leave and workplace accommodations have made it easier for mothers to breast feed, but even so, many women choose not to do so or engage in breast feeding for limited amounts of time. In a detailed review of this topic it was concluded that this method of feeding infants has multiple benefits (Jonas & Woodside, 2015). We’ve all heard that breast feeding may help bonding by causing the release of hormones, such as oxytocin, but it has multiple other important functions. Jonas and Woodside pointed out that breast milk contains nutrients such as fat, protein, vitamins, and minerals, and long chain polyunsaturated fatty acids that contribute to the development of cognitive and motor processes. Furthermore, breast milk contributes to growth factors and hormones that affect neurodevelopment, as well as immunoglobulins important to prevent some infections. As a result, relative to bottle-fed infants, those who were breast-fed were less likely to develop respiratory tract infections, problems associated with the gastrointestinal tract, obesity, diabetes, and childhood leukemia and lymphoma (e.g., Amitay & Keinan-Boker, 2015). Extended duration of breast feeding was also accompanied by enhanced cognitive abilities in children. Whether these effects stemmed from the biological changes that come from breast feeding or were secondary to other factors is uncertain.

It’s not just the infant who gains from breast feeding. Jonas and Woodside pointed to the benefits gained by the mom, including reduced risk of later breast and ovarian cancer, metabolic disorders, type 2 diabetes, and anxiety. These moms were also more sensitive to their children’s requests, reflected by brain changes elicited by the cries of their children. Furthermore, meta-analyses have pointed to this practice diminishing risk for several illnesses in moms, such as type 2 diabetes (e.g., Jäger et al., 2014). However, here again, intervening variables could influence the observed differences between breast- versus bottle-fed infants.

Not all scientists agree that breast is best, intimating that many studies supporting that view were beset by procedural problems. In general, white infants were more likely to be breast-fed than were black infants, which was linked to household income and education, and thus could have been the critical link to well-being. When these factors were controlled for in statistical models of data collected from the National Longitudinal Study of Youth, which tracked individuals from 1986 through to 2010, it seemed that the advantages of breast feeding were absent (Colen & Ramey, 2014).

Within the US, 75% of new mothers initially breast feed their children, but owing to several factors, by the time the child is 6 months of age, only 13% do so exclusively. Yet, both the World Health Organization and American Academy of Pediatrics recommend exclusive breast feeding for the first 6 months of life, and combined breast and formula feeding until 1 or 2 years of age. The US Surgeon General has provided a list of recommendations for mothers and employers so that breast feeding is facilitated (www.surgeongeneral.gov/library/calls/breastfeeding/index.html).

**Oxytocin**

The hormone oxytocin is released during childbirth as well lactation, and is thought to be important in mother–child attachment formation. Beyond this, oxytocin has also been implicated as being fundamental for other prosocial behaviors, such as love, generosity, altruism,
empathy, sacrifice, the motivation to be with others (social motivation), and even the ability to infer the emotions of others based on their facial cues (McQuaid et al., 2014). When oxytocin receptors are altered (through a gene polymorphism) individuals may be less responsive to socially-related environmental triggers (Cardoso, Orlando et al., 2014; Insel & Young, 2001), may see the world as more threatening, and might have a tendency to be less generous (Campbell, 2010).

There has been a considerable increase in public interest regarding oxytocin, fueled by the media, which refer to it as ‘the love hormone’. Given its role in social interactions, social identity, and trust (Kosfeld et al., 2005), this hormone may have a pronounced influence on many attributes related to interpersonal interactions as well as our abilities to use social factors in helping us deal with stressors. While not denying a role for oxytocin in promoting prosocial behaviors, as we’ll see in Chapter 5, it has been suggested that oxytocin may have a darker side in relation to behavioral outputs, depending on different contexts and interactions with other hormone and neurotransmitter processes (McQuaid et al., 2014).

GROWTH FACTORS

Growth factors (neurotrophins) comprise substances that are fundamental for cellular growth and proliferation, as well as cellular differentiation (the latter allows cells to become specialized and to engage in particular functions), and can promote the development and growth of new neurons (Huang & Reichardt, 2001). So, contrary to the long-held belief that whatever neurons you had at birth was the maximum you would ever have, there is the possibility that in some brain areas new cells can be born, although the number is likely to be relatively small. Still, if these cells could be encouraged to develop, then ways might be established to treat disorders that stem from neuronal loss.

The best known and most widely studied aspect of neurotrophins is their capacity to enhance neuroplasticity, generally referring to formation of synaptic connections and the strengthening of these connections owing to experiences, learning and memory, thinking, and emotional responses. With continued experiences these neurotrophins allow for increased communication between neurons and the creation of increasingly sophisticated neuronal networks. The most widely studied growth factor in relation to psychological processes is brain-derived neurotrophic factor (BDNF). This growth factor can be disturbed by environmental challenges, such as stressful events, and thus in addition to affecting memory processes it has been implicated in a variety of psychological disorders, such as depression and PTSD (Duman & Monteggia, 2006), which we’ll hear more about in Chapter 5.

Yet another growth factor, basic fibroblast growth factor (FGF-2), operates much like BDNF. This growth factor is also affected by stressful events, and may influence neurogenesis within the hippocampus, and could thus influence memory processes and mood states (Molteni et al., 2001). Numerous other growth factors have been identified, each of which has specific functions, although there is considerable overlap in what they do. Table 3.4 presents a listing of some of these growth factors and their presumed functions.
### Table 3.4  Growth factors

<table>
<thead>
<tr>
<th>Neurotrophin</th>
<th>Biological effect</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain-derived neurotrophic factor (BDNF)</td>
<td>Supports survival of neurons; encourages growth and differentiation of new neurons; promotes synaptic growth.</td>
<td>Influences memory processes, stress responses, mood states.</td>
</tr>
<tr>
<td>Basic fibroblast growth factor (bFGF or FGF-2)</td>
<td>Involved in neuroplasticity; formation of new blood vessels; protective actions in relation to heart injury; essential for maintaining stem cell differentiation.</td>
<td>Contributes to wound healing; neuroprotective; diminishes tissue death (e.g., following heart attack); related to anxiety and depression.</td>
</tr>
<tr>
<td>Nerve growth factor (NGF) and family members</td>
<td>Contributes to cell survival; growth and differentiation of new neurons. Fundamental for maintenance and survival of sympathetic and sensory neuron; axonal growth.</td>
<td>Survival of several types of neuron; new neuron formation from stem cells; related to neuron regeneration, myelin repair, and neurodegeneration. Implicated in cognitive functioning, inflammatory diseases, in several psychiatric disorders, addiction, dementia as well as in physical illness, such as heart disease, and diabetes.</td>
</tr>
<tr>
<td>Neurotrophin-3 (NT-3) and Neurotrophin-4 (NT-4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin-like growth factor 1 (IGF-1)</td>
<td>Secreted by the liver upon stimulation by growth hormone (GH).</td>
<td>Promotes cell proliferation and inhibits cell death (apoptosis).</td>
</tr>
<tr>
<td>Vascular endothelial growth factors (VEGF)</td>
<td>Signaling protein associated with the formation of the circulatory system (vasculogenesis) and the growth of blood vessels (angiogenesis).</td>
<td>Creates new blood vessels during embryonic development, encourages development of blood vessels following injury, and creates new blood vessels when some are blocked. Muscles stimulated following exercise. Implicated in various diseases, such as rheumatoid arthritis, and poor prognosis in relation to breast cancer.</td>
</tr>
</tbody>
</table>

### IMMUNE FUNCTIONING

The immune system’s job is that of protecting us from all sorts of potential foreign invaders in the form of bacteria, viruses, and a constellation of other microorganisms that seem intent on harming us. In order to be able to do its job effectively, the immune system needs to be able to distinguish
between what is part of the self from that which isn’t, and then get rid of the foreign particles. The immune system is capable and tough, but it’s obviously limited in some respects given that we often do develop illnesses. Viral and bacterial infections are common, as are endemic illnesses and epidemics, and the risk of pandemics seems to be a pervasive threat. Cancers appear to be able to get around our immune defenses, diseases such as HIV/AIDS do their dirty work by causing our immune response to be compromised, allergic reactions occur when aspects of our immune system become too pronounced, and sometimes our own immune system, like a traitorous best friend, can turn on us so that an autoimmune disorder develops (i.e., where the immune system attacks the self). Some people seem to have particularly effective immune systems that are well equipped to deal with challenges, but what is it that makes them this way? Is this connected to the genes inherited or to life-style factors? Do neurotransmitter and hormonal processes affect immune functioning, and does immune functioning also affect CNS processes and hence encourage the development of psychological disorders?

How the immune system operates

To consider these questions, an understanding of how the immune system works is necessary, even if this is at a very rudimentary level. The immune system is often described as being analogous to an army equipped with different regiments that go into the battle at different times. Some troops, based on their experience, are responsible for recognizing the enemy and also recognizing the self so that attacks aren’t misdirected (friendly fire). Troops are needed at the front lines with the intent of slowing down the enemy advance, and more specialized, stronger troops are brought up to go into the battle should the first line of defense be breached. Communication between different cells within the immune system is necessary so that more troops can be brought to the front lines, so that they enter the battle at the right time, and so that they disengage and return to the barracks once the battle is won.

Innate and acquired immunity

The immune system begins to develop prenatally, and at birth can fend off some challenges, although immune system functioning still has some way to go before it’s ready for a ruthless environment filled with multiple threats. During the course of prenatal development, immune cells learn about tissues that are part of the self, and thus when they encounter foreign particles postnatally, their ‘innate immunity’ is critical in identifying what’s part of the self and, by exclusion, what is foreign (e.g., Medzhitov, 2007). After birth, as immune cells come into contact with foreign materials, further learning occurs about foreign matter, which is referred to as ‘adaptive’ or ‘acquired’ immunity (Pancer & Cooper, 2006). When our immune cells first encounter a virus we might become ill as it takes some time for an immune response to be mounted and the enemy engaged. However, having learned about foreign particles (antigens), should they again be encountered, a greater and faster immune response (secondary immune response) is mounted so that the virus is destroyed before we become ill (Janeway et al., 2005).

Monocytes, neutrophils and macrophage

Travelling through our bodies are several types of white blood cells responsible for identifying and destroying foreign particles (Roitt et al., 2001). Of these, neutrophils and monocytes, which
are particularly abundant, respond quickly to bacteria. Monocytes will leave the bloodstream and convert to *macrophages*, which remove dead cells as well as attacking and engulfing microorganisms, a process referred to as *phagocytosis*. After gobbling up foreign particles, macrophages break them down and present a portion of them to other immune cells (e.g., *lymphocytes*), some of which have the capability of recognizing whether or not the particle is foreign.

**Lymphocytes**

Lymphocytes come in several varieties, including T and B cells formed in the thymus and bone marrow, respectively. In addition, they are present in lymph nodes, spleen, and lungs, which serve as secondary lymphoid organs. One form of T cell, the *T helper (Th)* cell, is responsible for recognizing the foreign particles presented to them by macrophages. Once this recognition has occurred, the *Th*$_1$ cells (a form of Th cell) will inform *T cytotoxic* cells of this, causing them to multiply rapidly (this is what causes glands to swell) and then act against the virus. Being devious, viruses ordinarily infiltrate body cells and use their machinery to multiply within the cell, after which they burst forth to infect other cells. To counter this, T cells will bind with infected cells, rupture the cellular membrane and inject enzymes into it (a processes referred to as *lysis*), thereby causing the viral contents to be destroyed. Thus, when this ‘*cellular*’ immune response is instigated, T cells are destroying whole factories of virus producers. Once the job of getting rid of the foreign particle has been completed, yet another type of T cell, referred to as Treg cells, are responsible for getting cytotoxic T cells to stop their attacks. At the same time, certain Th cells, notably Th$_2$ cells, release anti-inflammatory cytokines that act against the pro-inflammatory actions that had been instigated by Th$_1$ cells.

In addition to destroying invaders through T cytotoxic cells, Th cells also excite *B cells* which multiply prodigiously and go into battle to fend against foreign invaders. The B cells do this through the production of *antibodies* or *immunoglobulin* molecules (abbreviated Ig) that recognize foreign particles based on earlier experiences, trap and mark them, and then call upon other agents (*complement factors*) to help complete the job of destroying them. This process is frequently called *humoral immunity* because the substrates involved in this immune response are found in body fluids (or humors). The B cells secrete several classes of immunoglobulin molecules (IgA, IgD, IgE, IgM, and IgG) that have somewhat different functions, reside in different places, and are called upon at different times. Thus, they differ with respect to which antibodies meet antigens first and, correspondingly, they are activated at different times over the course of an immune response being mounted.

**Natural killer (NK) cells**

Yet another type of immune cell that acts like a front-line defender is the *natural killer (NK)* cell, which seem to have learned about the self during prenatal development. These cells travel through the body just as T cells do, and serve to destroy virally infected cells or those that have become cancerous. These aren’t the strongest immune cells, despite their threatening name, but are fundamental in keeping infection from becoming excessive, thus allowing for the build-up of more powerful T cells to come into action at an appropriate time.

**Immunological memory**

One of the most important features of T and B cells is that they may develop an *immunological memory* of a foreign particle that had been encountered. When this particle or one that is
sufficiently similar to it is again met some time later, a rapid and robust immune response is mounted so that the illness typically doesn’t develop. When T and B cells are primed or sensitized to respond in a particular way, they undergo clonal expansion (increased multiplication, also termed proliferation) and each of their progeny behave in the same particular way, thus leading to a powerful immune response. As well, passive immunity can occur, which comprises the transfer of humoral immunity as in the form of maternal antibodies from a pregnant woman to the fetus. There are instances, however, in which immune memory might not help us avoid illness. Specifically, a virus may be successful in hiding (e.g., within nerve cells) and may re-emerge at some later time, perhaps in a different form. For example, shingles (herpes zoster) may develop among those who had had chickenpox years earlier.

Figure 3.4 Following exposure to an antigen (or pathogen), an immune response is mounted. This comprises a rapid activation of natural killer cells, and a sequence of changes in which macrophages gobble up the foreign particles, digest them, and then present them to T helper cells that decide whether they are part of the self or a foreign substance. In the latter instance, T and B cells are informed, which then multiply. Activated T cells will mature and then destroy foreign particles present within cells, whereas B cells do so through secreting antibodies that bind with the antigen indirectly, causing its destruction. Once the threat is removed, another form of T helper cell, together with T regulatory cells (Treg), will act to quiet the immune response. Some of the T and B cells will retain a memory of the foreign particle so that a more rapid and stronger response is mounted should this threat reappear at a later time.

Cytokines

Just as neurons within the brain communicate with one another, so do immune cells, although the nature of the communication is less elaborate or sophisticated. Communication between these
cells occurs through the release of signaling molecules, cytokines, which are manufactured within immune cells and in brain microglia (O’Shea & Murray, 2008). In the periphery these cytokines cause the growth and differentiation of lymphocytes, and exert a regulatory effect on them (much like the growth factors discussed earlier). In the context of research related to health psychology, the best known cytokines are interleukin (IL)-1β, IL-6, tumor necrosis factor-α (TNF-α), and interferons (IFN), all of which encourage inflammation and are thus referred to as pro-inflammatory cytokines. Tight regulation of immune and cytokine functioning is essential given their role in our survival. The Goldilocks principle applies in this regard (not too hot, not too cold; not too little, not too much), and immune functioning is managed through the balance of pro- and anti-inflammatory cytokines (e.g., IL-4 and IL-10), which vary over the course of an infection. Pro-inflammatory cytokines ought to predominate initially and during the main part of infection, but once the foreign particles have been eliminated, anti-inflammatory cytokines should become more prevalent in an effort to dissuade T cells from continuing in an attack mode.

**Cytokine–endocrine interactions**

Immune functioning is also regulated through the influence of various hormonal processes. Endocrine and immune factors signal one another, and reciprocal balances exist to keep their functioning within a particular range (Blalock, 1994). In this regard, cortisol, the hormone that is integral to the stress response, plays an especially significant role. It is activated by inflammatory stimuli and, conversely, it can dampen inflammatory immune functioning (Sternberg, 2006). When cortisol is increased, but remains within physiological levels, meaning it is within the ‘normal’ range observed in response to challenges, it sets a cap on immune functioning so that it doesn’t become excessive. At pharmacological levels, induced by exogenous administration of the hormone (or drug treatments), the considerably higher cortisol levels may have an immuno-suppressive action. Thus, alone or in combination with other agents, it has been used in treating illnesses where high levels of immune system actions are harmful. Cortisol isn’t alone in serving in this regulatory capacity; epinephrine, CRH, melanocortin, thyroid hormones, as well as estrogen and progesterone all have immunomodulatory actions (Blalock, 2005).

**Cytokine–brain interactions**

It had long been thought that the brain was ‘immunologically privileged’ in the sense that it was independent of immune functioning. However, just as CNS processes may come to affect immune functioning, an activated immune system may influence brain functioning. Immune cells can communicate with the brain through cytokines, which, despite their large size, directly or indirectly affect neurotransmission (Nadeau & Rivest, 1999). Indeed, in several respects the actions of inflammatory factors on brain functioning are akin to the effects of stressful events. This has contributed to the suggestion that the brain interprets peripheral immune challenges as if they were stressors, thereby promoting symptoms of mood and anxiety-related disorders as well as several neurological disturbances (Anisman & Merali, 1999). Cytokines appear within the brain (some more than others), possibly coming from the periphery, but they can also be generated by microglia resident within the CNS. In response to physical and chemical insults (e.g., concussion, seizure, cerebral ischemia, chemically induced brain lesions), and systemic challenge
with bacterial agents or viruses, as well as strong stressors, cytokine expression within the brain increases appreciably (Anisman et al., 2008). The increased cytokine presence might act in a protective or reparatory capacity; however, if their levels become excessively high, they might instead have destructive actions (Rothwell & Luheishi, 2000). The important point for the moment is that complex interactions exist among immune, hormonal, and brain neurochemical systems, which can then influence behavioral outcomes; and conversely, brain processes can affect each of these systems (Maier & Watkins, 1998).

**Challenges to immunological functioning**

There are occasions where the capacity of the immune system to protect us may be compromised. Chronic stressful experiences, for instance, could impair T, B, and NK cell multiplication, as well as their proficiency in eliminating foreign threats. Such effects can be elicited in animals by exposing them to predator odors, social aggression, or social instability, and in humans similar changes accompany psychologically stressful experiences, such as ostracism, relationship difficulties, job strain, and illness (Kemeny & Schedlowski, 2007; Slavich, Way et al., 2010).

It is hardly surprising that poor diet and loss of sleep may also affect immune system functioning and may thus contribute to the development or exacerbation of illnesses (Irwin, 2015). These life-style factors can also interact with stressful experiences to further influence the development of illness, and stressful events themselves will affect eating, sleep, and exercise, thereby making the effects of stressors that much worse. In Chapter 10 we’ll be dealing with illnesses associated with impaired immunity and we’ll come back to this topic in greater detail.

**THE ENTERIC NERVOUS SYSTEM AND THE MICROBIOME**

Our skin and immune factors that are present wherever entry to the body is possible (eyes, nose, mouth) protect us from the potential bad players that are lurking about. In a way, the good bacteria in the gut as well as immune factors that are present serve in a similar capacity. Stuff that gets to our tummy might not be all that clean, and bacteria that we have inherited (usually from mom during pregnancy and during actual delivery) serve as a barrier against microorganisms that threaten us.

**The enteric brain**

Within fields such as psychology and neuroscience, the focus of research has been on the brain and autonomic and immune systems, and much less attention had been devoted to the ‘enteric nervous system’, which refers to the nervous system associated with the gut. In fact, many people are surprised at the notion that there’s anything brain-related concerning the gut. Yet, the gut contains millions of neurons that communicate through many of the same neurotransmitters that are found in the brain. The enteric system runs through tissue that lines the esophagus, stomach, small intestine and colon, and is able to influence brain functioning, just as the brain influences
gut functioning (Gershon, 2000). Further, messages to the brain may occur through different routes, such as through stimulation of the *vagus nerve*, which extends from the viscera to the brain stem. Gut hormones, such as ghrelin, can also affect brain activity, thereby influencing hunger and obesity (Suzuki et al., 2010) and, as we saw earlier, may also influence mood and reward processes.

**Microbiota**

Our intestine isn’t a pristine place; it contains 100 trillion microorganisms of about 500–1,000 different bacterial species. The word ‘bacteria’ elicits negative connotations related to infection, and indeed some gut bacteria can be very bad for us, but some also come in a good form that keeps us well. Despite the great number of species that exist within the gut, about 30% comprise four key species – *B. thetaiotaomicron*, *B. vulgatus*, *B. distasonis*, and *B. fragilis* – which are probably particularly important in determining well-being (Sears, 2005). Gut bacteria are involved in the digestion of foods – including those that the stomach and gut couldn’t effectively digest, fighting against microorganisms that could produce negative consequences, the production of vitamin K, enhancement of fat storage, as well as contributing to the production of gut-associated lymphoid tissue and augmentation of immune functioning (Sears, 2005). Moreover, gut microbiota and its genome (*microbiome*) are fundamental in determining energy balance, and can affect several hormones, neurotransmitters, and immune factors. The metabolic functioning of gut microbiota is extensive and essential, to the extent that gut bacteria, collectively, have been referred to as ‘a forgotten organ’ (O’Hara & Shanahan, 2006).

The immune system in the gut has a tough balancing act to perform. On the one side it must respond to challenges in the form of pathogens, but on the other it must also be nonresponsive to food antigens and the microflora that are *commensal* (i.e., those bacteria that act in a positive symbiotic fashion with other factors). It seems likely that gut bacteria have evolved to maintain diversity, thereby increasing their ability to fight off a greater variety of bad bacteria that could appear, but concurrently act cooperatively with good bacteria. In fact, when times get tough (e.g., being in a low oxygen environment), gut bacteria even secrete substances that facilitate the survival of other bacterial species (Heinken & Thiele, 2015).

**Gut and immunity**

As in the case of so many of our other functions, multiple players are involved in shaping and maintaining intestinal immunity, including nutrition, short chain fatty acids, particular vitamins, cytokines, collaboration between specific types of immune cells, and commensal microflora (Spencer & Belkaid, 2012; Veldhoen & Brucklacher-Waldert, 2012). An animal can survive without the presence of gut bacteria, but their ability to withstand immunological challenges, for instance, will be markedly diminished (Rakoff-Nahoum et al., 2004). It also appears that among rodents born entirely germ-free, normal immune development that occurs postnatally is hindered, lymphoid disturbances will appear, and the balance between various aspects of the immune system will be thrown off, culminating in pathological vulnerabilities. In a like fashion, antibiotic treatments early in life can alter the microbiome and thus have long-term ramifications on well-being. Further, the vertical transmission of microbial protection that comes with vaginal
birth may be precluded through Caesarean delivery, thus leaving offspring vulnerable to illness (Peterson et al., 2015). There are, to be sure, several other elements that determine the microbial functioning of a newborn organism. This includes the specific foods that had been consumed by mom while she was pregnant as well as her general health and her use of medications, such as antibiotics.

It seems that a continuous battle persists between good bacteria in our gut and those that are harmful. Some of the good bacteria come from the food we eat and others are released by the epithelial cell layer (these line both the cavities and surfaces of structures), and even a modest increase shifts the balance to the good guys (Schluter & Foster, 2012). We are also blessed with a gene (dubbed SIGIRR), which stimulates immune responses that act against bad bacteria forming colonies that negatively affect health. However, disruptions of SIGIRR by antibiotics can cause the battle for supremacy to move toward the bad bacteria (Sham et al., 2013).

**Illnesses related to microbiota alterations**

When the balance between good and bad bacteria favors the bad, metabolic dysfunctions can arise (e.g., insulin resistance), inflammatory bowel disorder can be provoked (Sanz et al., 2015), as can colorectal cancer (Louis et al., 2014). The influence of gut bacteria doesn’t stop there, having been implicated in other disturbances ranging from chronic fatigue syndrome, fibromyalgia, mood disorders, alcoholism, and heart disease (Galland, 2014). Bacterial enzymes can also produce metabolites, such as D-lactic acid and ammonia, which can be toxic to neurons. It has also been reported that about 90% of the serotonin found in our periphery (only a small portion exists in the brain where it acts as a neurotransmitter) is formed in the digestive tract, some of which is made by bacteria (Yano et al., 2015). The peripheral serotonin may play a role in the promotion of illnesses such as irritable bowel syndrome, osteoporosis, and heart disease. Similarly, eating disorders, such as anorexia nervosa and bulimia, are influenced by specific proteins made by bacteria that affect eating (Tennoune et al., 2015).

Fortunately, *probiotics* (ingested microorganisms believed to have beneficial effects) and *prebiotics* (chemicals that promote the growth of microorganisms) can attenuate chronic disorders of the gut (DuPont & DuPont, 2011), and can influence obesity and metabolic syndrome (Delzenne et al., 2011). For that matter, changes of gut bacteria early in life can have persistent effects on health. For instance, when female mice that were genetically at risk for type 1 diabetes were treated with normal gut bacteria from adult mice, the likelihood of diabetes developing was reduced by 85%. This was accompanied by an increase of testosterone (which it will be recalled is present in females, although to a lesser extent than in males), and appeared to be essential for the effects of the gut bacterial treatment to be effective (Markle et al., 2013). It is of interest, as well, that gut bacteria can be passed from a mom to her child (e.g., through breast feeding). In a pregnant woman, good gut bacteria can affect those present in the fetus but, by the same token, among pregnant women using antibiotics, the loss of good bacteria will be felt by both mom and the fetus. During delivery the infant obtains further good bacteria present in the mom’s birth canal, and it has been maintained that differences are apparent between babies born vaginally and those born through C-section, which can have lasting health repercussions (Bäckhed et al., 2015).
ANTIBIOTIC JEOPARDY

Antibiotics have been used for decades to deal with bacterial infections. These were at one time the wonder drugs that could do what no other drug could, but their effectiveness has diminished as increasingly more bacteria have become resistant to these agents. There’s a second issue that needs to be considered in relation to the effects of antibiotics, namely that they not only kill potentially harmful bacteria, but also destroy good bacteria. When the balance of these bacteria shifts to the bad side, vulnerability to infection is increased. One particular condition, Clostridium difficile (C. difficile) infection has become rampant, most often appearing among hospital patients who had been treated with antibiotics. C. difficile is not uncommon, with 3 million new cases being reported each year, accompanied by 100,000 deaths, and has become increasingly more frequent within the community (i.e., outside hospitals). Several antibiotics can be used to treat C. difficile, such as Metronidazole and vancomycin, with about comparable efficacy (Drekonja et al., 2011), but the problem may reoccur. New treatments may be around the corner, at least based on animal studies in which two immunization treatments mustered a strong response by anti-toxin antibodies (Baliban et al., 2014).

Probiotics have become increasingly popular, so that some people might choose to use natural probiotic treatments to eliminate C. difficile, but in general this strategy isn’t particularly useful, and is not recommended for use, even as an add-on to standard medication (Pillai & Nelson, 2008). Not long ago, variants of C. difficile emerged that were more destructive and were resistant to some antibiotics, probably owing to people overusing antibacterial agents. In these cases, fecal microbiota obtained from a healthy donor are transplanted (in a liquefied and purified form, most often by colonoscopy or through the nasogastric route) to the affected individual, thereby reestablishing the colony of good bacteria, leading to success almost 90% of the time (Brandt et al., 2011). For those who are squeamish about treatment through colonoscopy or through a nasogastric tube, new delivery methods involving acid-resistant capsules have allowed for oral administration (Youngster et al., 2014). It seems, however, that full fecal transplants might not be needed as a small set of bacteria that alter the composition of bile acids may be sufficient to do the trick. Specifically, a cocktail containing the bacteria C. scindens and three other bacteria that partially attenuate C. difficile, effectively eliminated C. difficile (Buffie et al., 2015). So, that’s the poop on this issue.

There is some good news in our war against bacteria. Perhaps more companies will come out against using animals loaded with antibiotics, people might become more educated and stop using antibiotics when they get the sniffles, especially as antibiotics don’t work against viruses, and thus antibiotic resistance might develop less readily. Better antibiotics might also be created, although many drug companies have dropped out of the antibiotic chase. There may also be changes afoot as to how antibiotic resistance is determined and infections treated. Ordinarily, this amounts to (Continued)
taking some material from an infected area (or from blood or urine) and allowing resident bacteria to multiply in the presence of particular antibiotics. If they don’t multiply, then the antibacterial agent will likely be a good one to treat the infection. However, if bacteria continue to multiply irrespective of the antibiotic present, then we’re dealing with a resistant strain. This is all fine, except that it takes 16–24 hours to obtain results. New technologies allow for this to be reduced to 3–4 hours by determining whether antibiotics cause bacterial structure to change (Choi et al., 2014). If this approach pans out, same-day treatment will be possible for people with some sort of infection.

SUMMARY

The many behaviors in which we engage involve intricate and sensitive communication between neuronal processes. This is evident in the varied neurotransmitter functions that occur within and between brain regions, as well as interactions with hormone systems and the autonomic nervous system. It’s also clear that considerable communication occurs between the brain and the immune system, and in this regard mood states and other stress responses could affect immune ability, and, conversely, immunological processes can affect brain functioning. Even gut-related systems have been considered to be a player in the complex interactions that govern immune, endocrine, and brain functioning, and thus behavioral outputs.

As we’ll see in ensuing chapters, the functioning of these highly integrated systems are influenced by multiple external factors (stressors, diet, psychosocial experiences). Although we often attempt to identify individual factors that contribute to health disturbances, and then develop psychological tools to attenuate them, the very fact that so many systems interact with one another should, if nothing else, point to the complexities that are encountered in determining the development and course of illnesses, as well as how to attenuate them through behavioral methods. There are many routes by which environmental factors can impact endogenous processes leading to a pathological condition, and, as a result, a given treatment may be effective in attenuating symptoms of an illness in some individuals or under some condition, but not others.