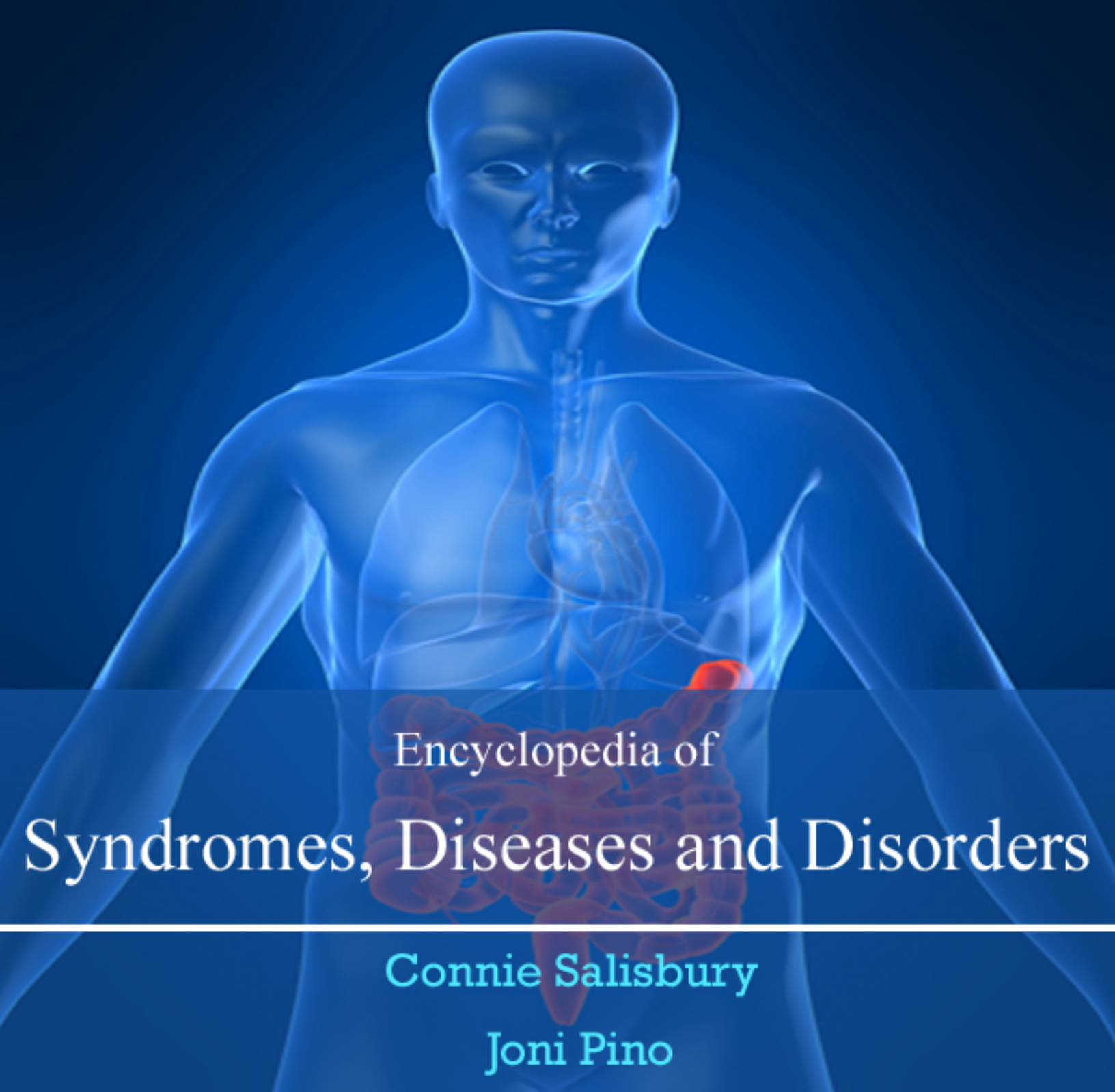

# Encyclopedia of Syndromes, Diseases and Disorders

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First Edition, 2012

ISBN 978-81-323-1390-8



*Published by:*
**College Publishing House**
4735/22 Prakashdeep Bldg,
Ansari Road, Darya Ganj,
Delhi - 110002
Email: info@wtbooks.com

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# Chapter 1

# Tourette Syndrome

| Tourette syndrome |
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Georges Gilles de la Tourette

(1857–1904)

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|---|---|
| **ICD-10** | F95.2 |
| **ICD-9** | 307.23 |
| **OMIM** | 137580 |
| **DiseasesDB** | 5220 |
| **MedlinePlus** | 000733 |
| **eMedicine** | med/3107 neuro/664 |
| **MeSH** | D005879 |

**Tourette syndrome** (also called **Tourette's syndrome**, **Tourette's disorder**, **Gilles de la Tourette syndrome**, **GTS** or, more commonly, simply **Tourette's** or **TS**) is an inherited neuropsychiatric disorder with onset in childhood, characterized by multiple physical (motor) tics and at least one vocal (phonic) tic; these tics characteristically wax

and wane. Tourette's is defined as part of a spectrum of tic disorders, which includes transient and chronic tics.

Tourette's was once considered a rare and bizarre syndrome, most often associated with the exclamation of obscene words or socially inappropriate and derogatory remarks (coprolalia), but this symptom is present in only a small minority of people with Tourette's. Tourette's is no longer considered a rare condition, but it may not always be correctly identified because most cases are classified as mild. Between 1 and 10 children per 1,000 have Tourette's; as many as 10 per 1,000 people may have tic disorders, with the more common tics of eye blinking, coughing, throat clearing, sniffing, and facial movements. Tourette's does not adversely affect intelligence or life expectancy . The severity of the tics decreases for most children as they pass through adolescence, and extreme Tourette's in adulthood is a rarity. Notable individuals with Tourette's are found in all walks of life.

Genetic and environmental factors play a role in the etiology of Tourette's, but the exact causes are unknown. In most cases, medication is unnecessary. There is no effective medication for every case of tics, but there are medications and therapies that can help when their use is warranted. Explanation and reassurance alone are often sufficient treatment; education is an important part of any treatment plan.

The eponym was bestowed by Jean-Martin Charcot (1825–1893) on behalf of his resident, Georges Albert Édouard Brutus Gilles de la Tourette (1859–1904), a French physician and neurologist, who published an account of nine patients with Tourette's in 1885.

## *Classification*

Tics are sudden, repetitive, stereotyped, nonrhythmic movements (motor tics) and utterances (phonic tics) that involve discrete muscle groups. Motor tics are movement-based tics, while phonic tics are involuntary sounds produced by moving air through the nose, mouth, or throat.

Tourette's is one of several tic disorders, which are classified by the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) according to type (motor or phonic tics) and duration (transient or chronic). Transient tic disorder consists of multiple motor tics, phonic tics or both, with a duration between four weeks and twelve months. Chronic tic disorder is either single or multiple, motor or phonic tics (but not both), which are present for more than a year. Tourette's is diagnosed when multiple motor tics, and at least one phonic tic, are present for more than a year. Tic disorders are defined similarly by the World Health Organization (International Statistical Classification of Diseases and Related Health Problems, ICD-10 codes).

Although Tourette's is the more severe expression of the spectrum of tic disorders, most cases are mild. The severity of symptoms varies widely among people with Tourette's, and mild cases may be undetected.

## *Characteristics*

Tics are movements or sounds "that occur intermittently and unpredictably out of a background of normal motor activity", having the appearance of "normal behaviors gone wrong". The tics associated with Tourette's change in number, frequency, severity and anatomical location. Waxing and waning—the ongoing increase and decrease in severity and frequency of tics—occurs differently in each individual. Tics also occur in "bouts of bouts", which vary for each person.

Coprolalia (the spontaneous utterance of socially objectionable or taboo words or phrases) is the most publicized symptom of Tourette's, but it is not required for a diagnosis of Tourette's and only about 10% of Tourette's patients exhibit it. Echolalia (repeating the words of others) and palilalia (repeating one's own words) occur in a minority of cases, while the most common initial motor and vocal tics are, respectively, eye blinking and throat clearing.

Examples of motor tics

In contrast to the abnormal movements of other movement disorders (for example, choreas, dystonias, myoclonus, and dyskinesias), the tics of Tourette's are stereotypic, temporarily suppressible, nonrhythmic, and often preceded by an unwanted premonitory urge. Immediately preceding tic onset, most individuals with Tourette's are aware of an urge, similar to the need to sneeze or scratch an itch. Individuals describe the need to tic as a buildup of tension, pressure, or energy which they consciously choose to release, as if they "had to do it" to relieve the sensation or until it feels "just right". Examples of the premonitory urge are the feeling of having something in one's throat, or a localized discomfort in the shoulders, leading to the need to clear one's throat or shrug the shoulders. The actual tic may be felt as relieving this tension or sensation, similar to scratching an itch. Another example is blinking to relieve an uncomfortable sensation in the eye. These urges and sensations, preceding the expression of the movement or

vocalization as a tic, are referred to as "premonitory sensory phenomena" or premonitory urges. Because of the urges that precede them, tics are described as semi-voluntary or "*unvoluntary*", rather than specifically *involuntary*; they may be experienced as a *voluntary*, suppressible response to the unwanted premonitory urge. Published descriptions of the tics of Tourette's identify sensory phenomena as the core symptom of the syndrome, even though they are not included in the diagnostic criteria.

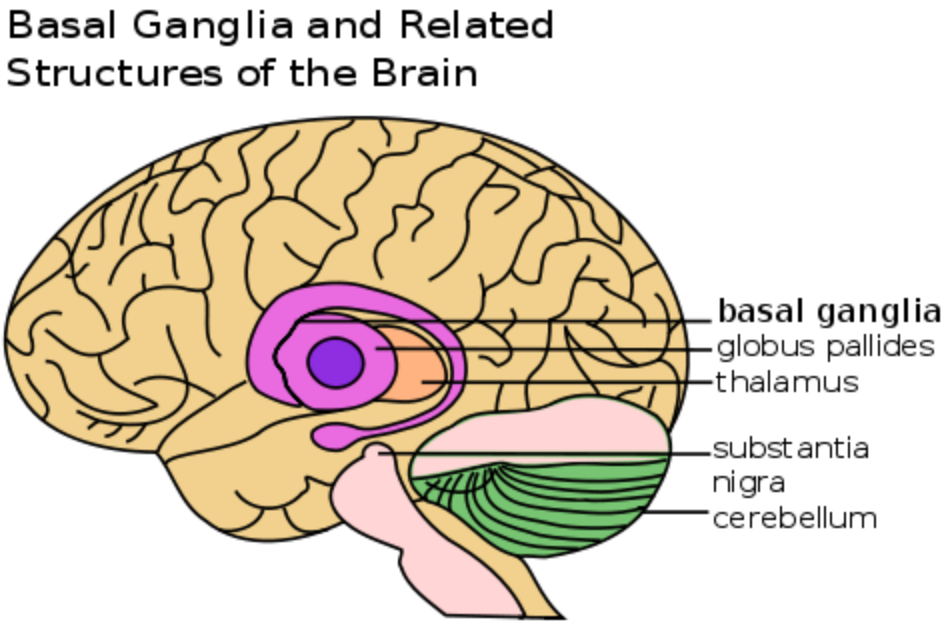
While individuals with tics are sometimes able to suppress their tics for limited periods of time, doing so often results in an explosion of tics afterward. People with Tourette's may seek a secluded spot to release their symptoms, or there may be a marked increase in tics after a period of suppression at school or at work. Some people with Tourette's may not be aware of the premonitory urge. Children may be less aware of the premonitory urge associated with tics than are adults, but their awareness tends to increase with maturity. They may have tics for several years before becoming aware of premonitory urges. Children may suppress tics while in the doctor's office, so they may need to be observed while they are not aware they are being watched. The ability to suppress tics varies among individuals, and may be more developed in adults than children.

Although there is no such thing as a "typical" case of Tourette syndrome, the condition follows a fairly reliable course in terms of the age of onset and the history of the severity of symptoms. Tics may appear up to the age of eighteen, but the most typical age of onset is from five to seven. A 1998 study published by Leckman *et al.* of the Yale Child Study Center showed that the ages of highest tic severity are eight to twelve (average ten), with tics steadily declining for most patients as they pass through adolescence. The most common, first-presenting tics are eye blinking, facial movements, sniffing and throat clearing. Initial tics present most frequently in midline body regions where there are many muscles, usually the head, neck and facial region. This can be contrasted with the stereotyped movements of other disorders (such as stims and stereotypies of the autism spectrum disorders), which typically have an earlier age of onset, are more symmetrical, rhythmical and bilateral, and involve the extremities (e.g., flapping the hands). Tics that appear early in the course of the condition are frequently confused with other conditions, such as allergies, asthma, and vision problems: pediatricians, allergists and ophthalmologists are typically the first to see a child with tics.

Among patients whose symptoms are severe enough to warrant referral to clinics, obsessive–compulsive disorder (OCD) and attention-deficit hyperactivity disorder (ADHD) are often associated with Tourette's. Not all persons with Tourette's have ADHD or OCD or other comorbid conditions (co-occurring diagnoses other than Tourette's), although in clinical populations, a high percentage of patients presenting for care do have ADHD. One author reports that a ten-year overview of patient records revealed about 40% of patients with Tourette's have "TS-only" or "pure TS", referring to Tourette syndrome in the absence of ADHD, OCD and other disorders. Another author reports that 57% of 656 patients presenting with tic disorders had uncomplicated tics, while 43% had tics plus comorbid conditions. "Full-blown Tourette's" is a term used to describe patients who have significant comorbid conditions in addition to tics.

## *Causes*

The exact cause of Tourette's is unknown, but it is well established that both genetic and environmental factors are involved. Genetic studies have shown that the overwhelming majority of cases of Tourette's are inherited, although the exact mode of inheritance is not yet known, and no gene has been identified. In some cases, Tourette's is *sporadic*, that is, it is not inherited from parents. In other cases, tics are associated with disorders other than Tourette's, a phenomenon known as *tourettism*.




Brain structures implicated in Tourette syndrome

A person with Tourette's has about a 50% chance of passing the gene(s) to one of his or her children, but Tourette's is a condition of variable expression and incomplete penetrance. Thus, not everyone who inherits the genetic vulnerability will show symptoms; even close family members may show different severities of symptoms, or no symptoms at all. The gene(s) may express as Tourette's, as a milder tic disorder (transient or chronic tics), or as obsessive–compulsive symptoms without tics. Only a minority of the children who inherit the gene(s) have symptoms severe enough to require medical attention. Gender appears to have a role in the expression of the genetic vulnerability: males are more likely than females to express tics.

Non-genetic, environmental, infectious, or psychosocial factors—while not causing Tourette's—can influence its severity. Autoimmune processes may affect tic onset and exacerbation in some cases. In 1998, a team at the US National Institute of Mental Health proposed a hypothesis that both obsessive–compulsive disorder (OCD) and tic disorders may arise in a subset of children as a result of a poststreptococcal autoimmune process. Children who meet five diagnostic criteria are classified, according to the hypothesis, as

having Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infections (PANDAS). This contentious hypothesis is the focus of clinical and laboratory research, but remains unproven.

The exact mechanism affecting the inherited vulnerability to Tourette's has not been established, and the precise etiology is unknown. Tics are believed to result from dysfunction in cortical and subcortical regions, the thalamus, basal ganglia and frontal cortex. Neuroanatomic models implicate failures in circuits connecting the brain's cortex and subcortex, and imaging techniques implicate the basal ganglia and frontal cortex.

Some forms of OCD may be genetically linked to Tourette's. A subset of OCD is thought to be etiologically related to Tourette's and may be a different expression of the same factors that are important for the expression of tics. The genetic relationship of ADHD to Tourette syndrome, however, has not been fully established.

## *Diagnosis*

According to the revised fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR), Tourette's may be diagnosed when a person exhibits both multiple motor and one or more vocal tics (although these do not need to be concurrent) over the period of a year, with no more than three consecutive tic-free months. The previous DSM-IV included a requirement for "marked distress or significant impairment in social, occupational or other important areas of functioning", but this requirement was removed in the most recent update of the manual, in recognition that clinicians see patients who meet all the other criteria for Tourette's, but do not have distress or impairment. The onset must have occurred before the age of 18, and cannot be attributed to the "direct physiological effects of a substance or a general medical condition". Hence, other medical conditions that include tics or tic-like movements—such as autism or other causes of tourettism—must be ruled out before conferring a Tourette's diagnosis.

There are no specific medical or screening tests that can be used in diagnosing Tourette's; it is frequently misdiagnosed or underdiagnosed, partly because of the wide expression of severity, ranging from mild (the majority of cases) or moderate, to severe (the rare, but more widely-recognized and publicized cases). Coughing, eye blinking and tics that mimic asthma are commonly misdiagnosed.

The diagnosis is made based on observation of the individual's symptoms and family history, and after ruling out secondary causes of tic disorders. In patients with a typical onset and a family history of tics or obsessive–compulsive disorder, a basic physical and neurological examination may be sufficient.

There is no requirement that other comorbid conditions (such as ADHD or OCD) be present, but if a physician believes that there may be another condition present that could explain tics, tests may be ordered as necessary to rule out that condition. An example of this is when diagnostic confusion between tics and seizure activity exists, which would

call for an EEG, or if there are symptoms that indicate an MRI to rule out brain abnormalities. TSH levels can be measured to rule out hypothyroidism, which can be a cause of tics. Brain imaging studies are not usually warranted. In teenagers and adults presenting with a sudden onset of tics and other behavioral symptoms, a urine drug screen for cocaine and stimulants might be necessary. If a family history of liver disease is present, serum copper and ceruloplasmin levels can rule out Wilson's disease. Most cases are diagnosed by merely observing a history of tics.

Secondary causes of tics (not related to inherited Tourette syndrome) are commonly referred to as tourettism. Dystonias, choreas, other genetic conditions, and secondary causes of tics should be ruled out in the differential diagnosis for Tourette syndrome. Other conditions that may manifest tics or stereotyped movements include developmental disorders, autism spectrum disorders, and stereotypic movement disorder; Sydenham's chorea; idiopathic dystonia; and genetic conditions such as Huntington's disease, neuroacanthocytosis, Hallervorden-Spatz syndrome, Duchenne muscular dystrophy, Wilson's disease, and tuberous sclerosis. Other possibilities include chromosomal disorders such as Down syndrome, Klinefelter's syndrome, XYY syndrome and fragile X syndrome. Acquired causes of tics include drug-induced tics, head trauma, encephalitis, stroke, and carbon monoxide poisoning. The symptoms of Lesch-Nyhan syndrome may also be confused with Tourette syndrome. Most of these conditions are rarer than tic disorders, and a thorough history and examination may be enough to rule them out, without medical or screening tests.

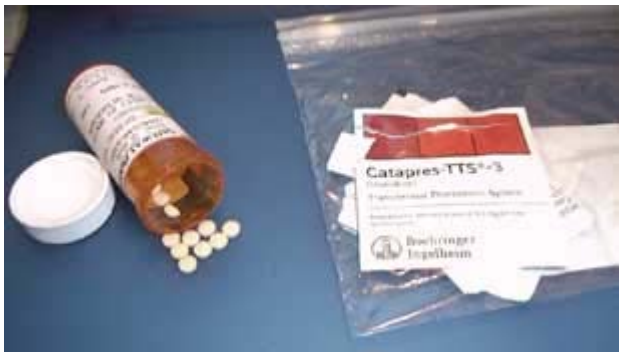
## *Screening*

Although not all people with Tourette's have comorbid conditions, most Tourette's patients presenting for clinical care at specialty referral centers may exhibit symptoms of other conditions along with their motor and phonic tics. Associated conditions include attention-deficit hyperactivity disorder (ADD or ADHD), obsessive–compulsive disorder (OCD), learning disabilities and sleep disorders. Disruptive behaviors, impaired functioning, or cognitive impairment in patients with comorbid Tourette's and ADHD may be accounted for by the comorbid ADHD, highlighting the importance of identifying and treating comorbid conditions. Disruption from tics is commonly overshadowed by comorbid conditions that present greater interference to the child. Tic disorders in the absence of ADHD do not appear to be associated with disruptive behavior or functional impairment, while impairment in school, family, or peer relations is greater in patients who have more comorbid conditions and often determines whether therapy is needed.

Because comorbid conditions such as OCD and ADHD can be more impairing than tics, these conditions are included in an evaluation of patients presenting with tics. "It is critical to note that the comorbid conditions may determine functional status more strongly than the tic disorder," according to Samuel Zinner, MD. The initial assessment of a patient referred for a tic disorder should include a thorough evaluation, including a family history of tics, ADHD, obsessive–compulsive symptoms, and other chronic medical, psychiatric and neurological conditions. Children and adolescents with TS who have learning difficulties are candidates for psychoeducational testing, particularly if the

child also has ADHD. Undiagnosed comorbid conditions may result in functional impairment, and it is necessary to identify and treat these conditions to improve functioning. Complications may include depression, sleep problems, social discomfort and self-injury.

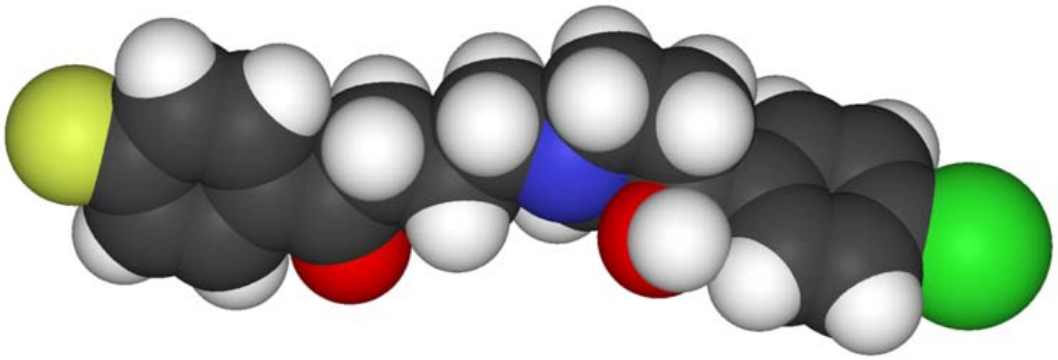
## *Management*




Clonidine (or the clonidine patch) is one of the medications typically tried first when medication is needed for Tourette's.

The treatment of Tourette's focuses on identifying and helping the individual manage the most troubling or impairing symptoms. Most cases of Tourette's are mild, and do not require pharmacological treatment; instead, psychobehavioral therapy, education, and reassurance may be sufficient. Treatments, where warranted, can be divided into those that target tics and comorbid conditions, which, when present, are often a larger source of impairment than the tics themselves. Not all people with tics have comorbid conditions, but when those conditions are present, they often take treatment priority.

There is no cure for Tourette's and no medication that works universally for all individuals without significant adverse effects. Knowledge, education and understanding are uppermost in management plans for tic disorders. The management of the symptoms of Tourette's may include pharmacological, behavioral and psychological therapies. While pharmacological intervention is reserved for more severe symptoms, other treatments (such as supportive psychotherapy or cognitive behavioral therapy) may help to avoid or ameliorate depression and social isolation, and to improve family support. Educating a patient, family, and surrounding community (such as friends, school, and church) is a key treatment strategy, and may be all that is required in mild cases.



Model of a haloperidol molecule. Haloperidol is an antipsychotic medication sometimes used to treat severe cases of Tourette's.

Medication is available to help when symptoms interfere with functioning. The classes of medication with the most proven efficacy in treating tics—typical and atypical neuroleptics including risperidone (trade name Risperdal), ziprasidone (Geodon), haloperidol (Haldol), pimozide (Orap) and fluphenazine (Prolixin)—can have long-term and short-term adverse effects. The antihypertensive agents clonidine (trade name Catapres) and guanfacine (Tenex) are also used to treat tics; studies show variable efficacy, but a lower side effect profile than the neuroleptics. Stimulants and other medications may be useful in treating ADHD when it co-occurs with tic disorders. Drugs from several other classes of medications can be used when stimulant trials fail, including guanfacine (trade name Tenex), atomoxetine (Strattera) and tricyclic antidepressants. Clomipramine (Anafranil), a tricyclic, and SSRIs—a class of antidepressants including fluoxetine (Prozac), sertraline (Zoloft), and fluvoxamine (Luvox)—may be prescribed when a Tourette's patient also has symptoms of obsessive–compulsive disorder. Several other medications have been tried, including nicotine patches, but evidence to support their use is unconvincing.

Because children with tics often present to physicians when their tics are most severe, and because of the waxing and waning nature of tics, it is recommended that medication not be started immediately or changed often. Frequently, the tics subside with explanation, reassurance, understanding of the condition and a supportive environment. When medication is used, the goal is not to eliminate symptoms: it should be used at the lowest possible dose that manages symptoms without adverse effects, given that these may be more disturbing than the symptoms for which they were prescribed.

Cognitive behavioral therapy (CBT) is a useful treatment when OCD is present, and there is increasing evidence supporting the use of habit reversal in the treatment of tics. Relaxation techniques, such as exercise, yoga or meditation, may be useful in relieving the stress that may aggravate tics, but the majority of behavioral interventions (such as relaxation training and biofeedback, with the exception of habit reversal) have not been systematically evaluated and are not empirically supported therapies for Tourette's.

## *Prognosis*

André Malraux (1901–1976) was a French author, adventurer and Minister of Culture who had Tourette syndrome. President Kennedy, Marie-Madeleine Lioux, Malraux, Jackie Kennedy and Vice President Johnson were photographed at the unveiling of the *Mona Lisa* at the National Gallery of Art, Washington, DC, in 1963.

Tourette syndrome is a spectrum disorder—its severity ranges over a spectrum from mild to severe. The majority of cases are mild and require no treatment. In these cases, the impact of symptoms on the individual may be mild, to the extent that casual observers might not know of their condition. The overall prognosis is positive, but a minority of children with Tourette syndrome have severe symptoms that persist into adulthood. A study of 46 subjects at 19 years of age found that the symptoms of 80% had minimum to mild impact on their overall functioning, and that the other 20% experienced at least a moderate impact on their overall functioning. The rare minority of severe cases can

inhibit or prevent individuals from holding a job or having a fulfilling social life. In a follow-up study of thirty-one adults with Tourette's, all patients completed high school, 52% finished at least two years of college, and 71% were full-time employed or were pursuing higher education.

Regardless of symptom severity, individuals with Tourette's have a normal life span. Although the symptoms may be lifelong and chronic for some, the condition is not degenerative or life-threatening. Intelligence is normal in those with Tourette's, although there may be learning disabilities. Severity of tics early in life does not predict tic severity in later life, and prognosis is generally favorable, although there is no reliable means of predicting the outcome for a particular individual. The gene or genes associated with Tourette's have not been identified, and there is no potential "cure". A higher rate of migraines than the general population and sleep disturbances are reported.

Several studies have demonstrated that the condition in most children improves with maturity. Tics may be at their highest severity at the time that they are diagnosed, and often improve with understanding of the condition by individuals and their families and friends. The statistical age of highest tic severity is typically between eight and twelve, with most individuals experiencing steadily declining tic severity as they pass through adolescence. One study showed no correlation with tic severity and the onset of puberty, in contrast with the popular belief that tics increase at puberty. In many cases, a complete remission of tic symptoms occurs after adolescence. However, a study using videotape to record tics in adults found that, although tics diminished in comparison with childhood, and all measures of tic severity improved by adulthood, 90% of adults still had tics. Half of the adults who considered themselves tic-free still displayed evidence of tics.

It is not uncommon for the parents of affected children to be unaware that they, too, may have had tics as children. Because Tourette's tends to subside with maturity, and because milder cases of Tourette's are now more likely to be recognized, the first realization that a parent had tics as a child may not come until their offspring is diagnosed. It is not uncommon for several members of a family to be diagnosed together, as parents bringing children to a physician for an evaluation of tics become aware that they, too, had tics as a child.

Tim Howard, goalkeeper for Everton F.C., says, "Tourette's Syndrome is not a problem. ... It doesn't affect me one way or another on or off the field."

Children with Tourette's may suffer socially if their tics are viewed as "bizarre". If a child has disabling tics, or tics that interfere with social or academic functioning, supportive psychotherapy or school accommodations can be helpful. Because comorbid conditions (such as ADHD or OCD) can cause greater impact on overall functioning than tics, a thorough evaluation for comorbidity is called for when symptoms and impairment warrant.

A supportive environment and family generally gives those with Tourette's the skills to manage the disorder. People with Tourette's may learn to camouflage socially inappropriate tics or to channel the energy of their tics into a functional endeavor. Accomplished musicians, athletes, public speakers, and professionals from all walks of life are found among people with Tourette's. Outcomes in adulthood are associated more with the perceived significance of having severe tics as a child than with the actual severity of the tics. A person who was misunderstood, punished, or teased at home or at school will fare worse than children who enjoyed an understanding and supportive environment.

## *Epidemiology*

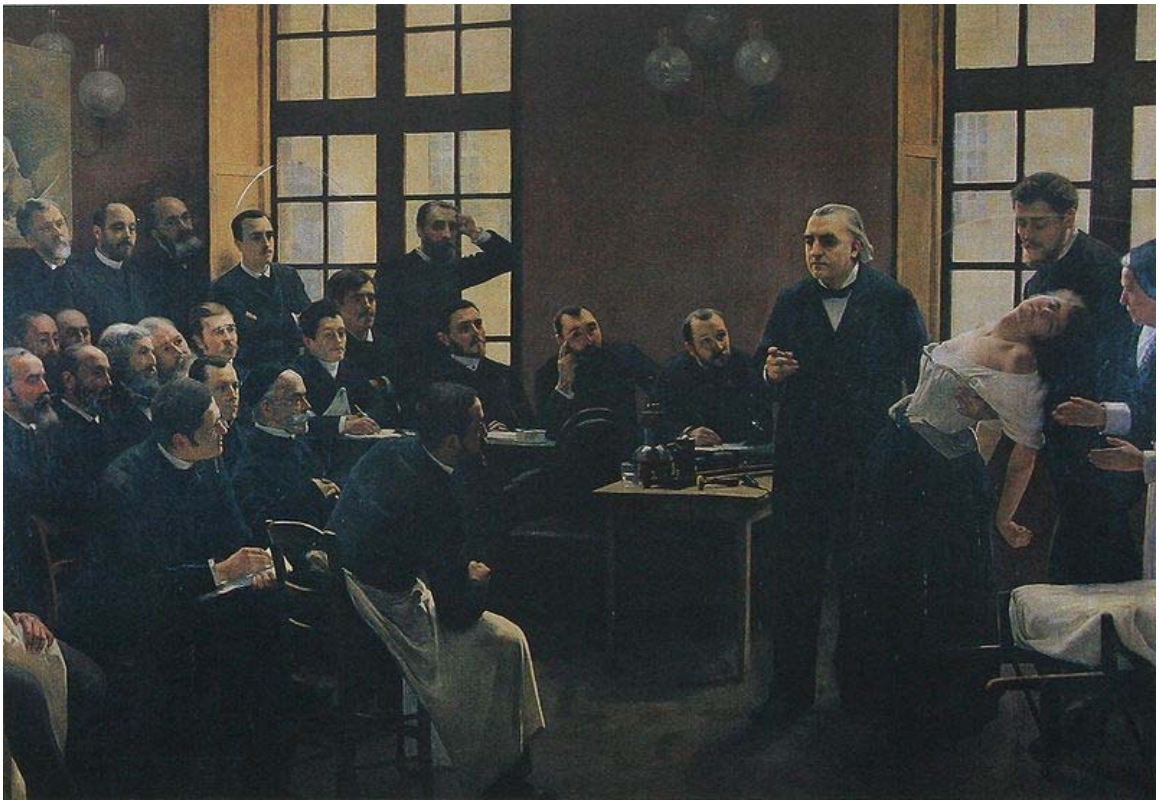
Tourette syndrome is found among all social, racial and ethnic groups, has been reported in all parts of the world, and is three to four times more frequent among males than

among females. The tics of Tourette syndrome begin in childhood and tend to remit or subside with maturity; thus, a diagnosis may no longer be warranted for many adults, and prevalence is much higher among children than adults. Children are five to twelve times more likely than adults to be identified as having tic disorders; as many as 1 in 100 people experience tic disorders, including chronic tics and transient tics in childhood. The emerging consensus is that 1–10 children per 1,000 have Tourette's, with several studies supporting a tighter range of 6–8 children per 1,000. Using year 2000 census data, a prevalence range of 1–10 per 1,000 yields an estimate of 53,000–530,000 school-age children with Tourette's in the US, and a prevalence estimate of 10 per 1,000 means that in 2001 about 553,000 people in the UK age 5 or older would have Tourette's. Most cases would be mild and almost unrecognizable in older individuals.

Tourette's is associated with several comorbid conditions, or co-occurring diagnoses, which are often the major source of impairment for an affected child. Among patients whose symptoms are severe enough to warrant referral to specialty Tourette's clinics, only a small minority have no other conditions, and obsessive–compulsive disorder (OCD) and attention-deficit hyperactivity disorder (ADHD) are often present. In children with Tourette's, ADHD is associated with functional impairment, disruptive behavior, and tic severity. Other comorbid conditions include self-injurious behaviors (SIB), anxiety, depression, personality disorders, oppositional defiant disorder, and conduct disorders. One author reports that a ten-year overview of patient records revealed about 40% of patients with Tourette's have "TS-only" or "pure TS", referring to Tourette syndrome in the absence of ADHD, OCD and other disorders.

Tourette syndrome was once thought to be rare: in 1972, the US National Institutes of Health (NIH) believed there were fewer than 100 cases in the United States, and a 1973 registry reported only 485 cases worldwide. However, multiple studies published since 2000 have consistently demonstrated that the prevalence is much higher than previously thought. Discrepancies across current and prior prevalence estimates come from several factors: ascertainment bias in earlier samples drawn from clinically referred cases, assessment methods that may fail to detect milder cases, and differences in diagnostic criteria and thresholds. There were few broad-based community studies published before 2000 and until the 1980s, most epidemiological studies of Tourette syndrome were based on individuals referred to tertiary care or specialty clinics. Children with milder symptoms are unlikely to be referred to specialty clinics, so these studies have an inherent bias towards more severe cases. Studies of Tourette syndrome are vulnerable to error because tics vary in intensity and expression, are often intermittent, and are not always recognized by clinicians, patients, family members, friends or teachers; approximately 20% of persons with Tourette syndrome do not recognize that they have tics. Recent studies—recognizing that tics may often be undiagnosed and hard to detect—use direct classroom observation and multiple informants (parent, teacher, and trained observers), and therefore record more cases than older studies relying on referrals. As the diagnostic threshold and assessment methodology have moved towards recognition of milder cases, the result is an increase in estimated prevalence.

## *History and research directions*



Jean-Martin Charcot (1825–1893) was a French neurologist and professor who bestowed the eponym for Tourette syndrome on behalf of his resident, Georges Albert Édouard Brutus Gilles de la Tourette. Charcot is shown here during a lesson with a "hysterical" woman patient at the Salpêtrière hospital.

The first presentation of Tourette syndrome is thought to be in a 1489 book, *Malleus maleficarum* ("Witch's hammer") by Jakob Sprenger and Heinrich Kraemer, describing a priest whose tics were "believed to be related to possession by the devil". A French doctor, Jean Marc Gaspard Itard, reported the first case of Tourette syndrome in 1825, describing Marquise de Dampierre, an important woman of nobility in her time. Jean-Martin Charcot, an influential French physician, assigned his resident Georges Albert Édouard Brutus Gilles de la Tourette, a French physician and neurologist, to study patients at the Salpêtrière Hospital, with the goal of defining an illness distinct from hysteria and from chorea.

In 1885, Gilles de la Tourette published an account of nine patients, *Study of a Nervous Affliction*, concluding that a new clinical category should be defined. The eponym was later bestowed by Charcot after and on behalf of Gilles de la Tourette.

Little progress was made over the next century in explaining or treating tics, and a psychogenic view prevailed well into the 20th century. The possibility that movement

disorders, including Tourette syndrome, might have an organic origin was raised when an encephalitis epidemic from 1918–1926 led to a subsequent epidemic of tic disorders.

During the 1960s and 1970s, as the beneficial effects of haloperidol (Haldol) on tics became known, the psychoanalytic approach to Tourette syndrome was questioned. The turning point came in 1965, when Arthur K. Shapiro—described as "the father of modern tic disorder research"—treated a Tourette's patient with haloperidol, and published a paper criticizing the psychoanalytic approach.

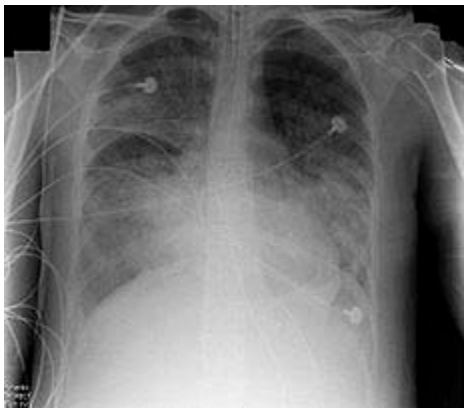
Since the 1990s, a more neutral view of Tourette's has emerged, in which biological vulnerability and adverse environmental events are seen to interact. In 2000, the American Psychiatric Association published the DSM-IV-TR, revising the text of DSM-IV to no longer require that symptoms of tic disorders cause distress or impair functioning.

Findings since 1999 have advanced TS science in the areas of genetics, neuroimaging, neurophysiology, and neuropathology. Questions remain regarding how best to classify Tourette syndrome, and how closely Tourette's is related to other movement disorders or psychiatric disorders. Good epidemiologic data is still lacking, and available treatments are not risk free and not always well tolerated. High-profile media coverage focuses on treatments that do not have established safety or efficacy, such as deep brain stimulation, and alternative therapies involving unstudied efficacy and side effects are pursued by many parents.

# Chapter 2

# Acute Respiratory Distress Syndrome

**Adult respiratory distress syndrome**



Chest x-ray of patient with ARDS

| | |
|---|---|
| **ICD-10** | J80. |
| **ICD-9** | 518.5, 518.82 |
| **DiseasesDB** | 892 |
| **MedlinePlus** | 000103 |
| **eMedicine** | med/70 |
| **MeSH** | D012128 |

**Acute respiratory distress syndrome** (**ARDS**), also known as **respiratory distress syndrome** (**RDS**) or **adult respiratory distress syndrome** (in contrast with IRDS) is a serious reaction to various forms of injuries to the lung.

ARDS is a severe lung disease caused by a variety of direct and indirect issues. It is characterized by inflammation of the lung parenchyma leading to impaired gas exchange with concomitant systemic release of inflammatory mediators causing inflammation, hypoxemia and frequently resulting in multiple organ failure. This condition is often fatal, usually requiring mechanical ventilation and admission to an intensive care unit. A less severe form is called acute lung injury (**ALI**).

ARDS formerly most commonly signified *adult respiratory distress syndrome* to differentiate it from infant respiratory distress syndrome in premature infants. However, as this type of pulmonary edema also occurs in children, *ARDS* has gradually shifted to mean *acute* rather than *adult*. The differences with the typical infant syndrome remain.

## *Definition*

### Historical background

Acute respiratory distress syndrome was first described in 1967 by Ashbaugh *et al.* Initially there was no definition, resulting in controversy over incidence and mortality. In 1988 an expanded definition was proposed which quantified physiologic respiratory impairment.

In 1994 a new definition was recommended by the American-European Consensus Conference Committee. It had two advantages: 1 it recognizes that severity of pulmonary injury varies, 2 it is simple to use.

ARDS was defined as the ratio of arterial partial oxygen tension ($PaO_2$) as fraction of inspired oxygen ($FiO_2$) below 200 mmHg in the presence of bilateral infiltrates on the chest x-ray. These infiltrates may appear similar to those of left ventricular failure, but the cardiac silhouette appears normal in ARDS. Also, the pulmonary capillary wedge pressure is normal (less than 18 mmHg) in ARDS, but raised in left ventricular failure.

A $PaO_2/FiO_2$ ratio less than 300 mmHg with bilateral infiltrates indicates acute lung injury (ALI). Although formally considered different from ARDS, ALI is usually just a precursor to ARDS.

### Consensus after 1967 and 1994

ARDS is characterized by:

- Acute onset
- Bilateral infiltrates on chest radiograph sparing costophrenic angles
- Pulmonary artery wedge pressure < 18 mmHg (obtained by pulmonary artery catheterization), if this information is available; if unavailable, then lack of clinical evidence of left ventricular failure suffices
- if $PaO_2$:$FiO_2$ < 300 mmHg (40 kPa) acute lung injury (ALI) is considered to be present
- if $PaO_2$:$FiO_2$ < 200 mmHg (26.7 kPa) acute respiratory distress syndrome (ARDS) is considered to be present

To summarize and simplify, ARDS is an acute (rapid onset) syndrome (collection of symptoms) that affects the lungs widely and results in a severe oxygenation defect, but is not heart failure

## *Signs and symptoms*

ARDS patients usually presents with shortness of breath, tachypnea and occasionally confusion resulting from low oxygen levels.

ARDS can occur within 24 to 48 hours of an injury (trauma, burns, aspiration, massive blood transfusion, drug/alcohol abuse) or an acute illness (infectious pneumonia, sepsis, acute pancreatitis).

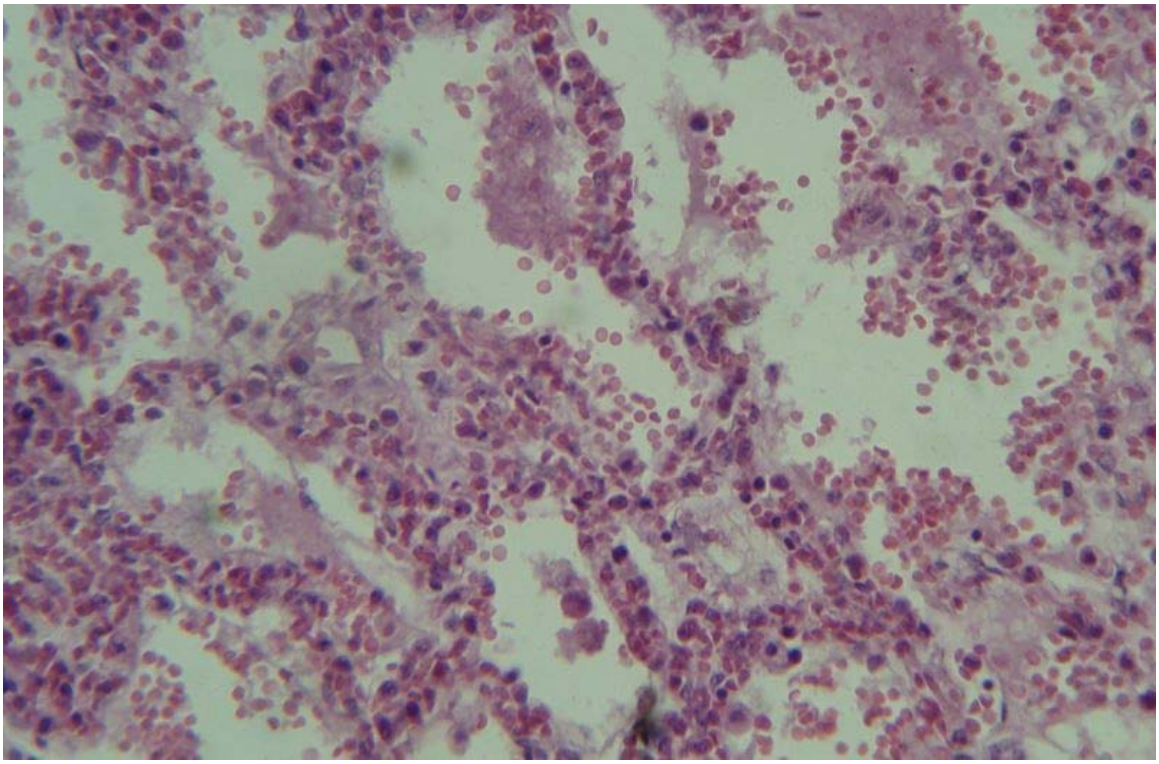
## *Diagnosis*

An arterial blood gas analysis and chest X-ray allow formal diagnosis by the aforementioned criteria. Although severe hypoxemia is generally included, the appropriate threshold defining abnormal $PaO_2$ has never been systematically studied. Note though, that a severe oxygenation defect is not synonymous with ventilatory support. Any $PaO_2$ below 100 (generally saturation less than 100%) on a supplemental oxygen fraction of 50% meets criteria for ARDS. This can easily be achieved by high flow oxygen supplementation without ventilatory support.

Any cardiogenic cause of pulmonary edema should be excluded. This can be done by placing a pulmonary artery catheter for measuring the pulmonary artery wedge pressure. However, this is not necessary and is now rarely done as abundant evidence has emerged demonstrating that the use of pulmonary artery catheters does not lead to improved patient outcomes in critical illness including ARDS.

Plain chest X-rays are sufficient to document bilateral alveolar infiltrates in the majority of cases. While CT scanning leads to more accurate images of the pulmonary parenchyma in ARDS, it has little utility in the clinical management of patients with ARDS, and remains largely a research tool.

## *Pathophysiology*



A pathohistological image of ARDS

ARDS is a clinical syndrome associated with a variety of pathological findings. These include pneumonia, eosinophilic pneumonia, cryptogenic organizing pneumonia, acute fibrinous organizing pneumonia, and diffuse alveolar damage (DAD). Of these, the pathology most commonly associated with ARDS is DAD.

DAD is characterized by a diffuse inflammation of lung parenchyma. The triggering insult to the parenchyma usually results in an initial release of cytokines and other inflammatory mediators, secreted by local epithelial and endothelial cells.

Neutrophils and some T-lymphocytes quickly migrate into the inflamed lung parynchema and contribute in the amplification of the phenomenon.

Typical histological presentation involves diffuse alveolar damage and hyaline membrane formation in alveolar walls.

Although the triggering mechanisms are not completely understood, recent research has examined the role of inflammation and mechanical stress.

## Inflammation

Inflammation alone, as in sepsis, causes endothelial dysfunction, fluid extravasation from the capillaries and impaired drainage of fluid from the lungs. Dysfunction of type II pulmonary epithelial cells may also be present, with a concomitant reduction in surfactant production. Elevated inspired oxygen concentration often becomes necessary at this stage, and may facilitate a 'respiratory burst' in immune cells.

In a secondary phase, endothelial dysfunction causes cells and inflammatory exudate to enter the alveoli. This pulmonary edema increases the thickness of the alveolo-capillary space, increasing the distance the oxygen must diffuse to reach blood. This impairs gas exchange leading to hypoxia, increases the work of breathing, eventually induces fibrosis of the airspace.

Moreover, edema and decreased surfactant production by type II pneumocytes may cause whole alveoli to collapse, or to completely flood. This *loss of aeration* contributes further to the right-to-left shunt in ARDS. As the alveoli contain progressively less gas, more blood flows through them without being oxygenated resulting in massive intrapulmonary shunting.

Collapsed alveoli (and small bronchi) do not allow gas exchange. It is not uncommon to see patients with a $PaO_2$ of 60 mmHg (8.0 kPa) despite mechanical ventilation with 100% inspired oxygen.

The loss of aeration may follow different patterns according to the nature of the underlying disease, and other factors. In pneumonia-induced ARDS, for example, large, more commonly causes relatively compact areas of alveolar infiltrates. These are usually distributed to the lower lobes, in their posterior segments, and they roughly correspond to the initial infected area.

In sepsis or trauma-induced ARDS, infiltrates are usually more patchy and diffuse. The posterior and basal segments are always more affected, but the distribution is even less homogeneous.

Loss of aeration also causes important changes in lung mechanical properties. These alterations are fundamental in the process of inflammation amplification and progression to ARDS in mechanically ventilated patients.

## Mechanical stress

Mechanical ventilation is an essential part of the treatment of ARDS. As loss of aeration (and the underlying disease) progress, the end tidal volume eventually grows to a level incompatible with life. Thus, mechanical ventilation is initiated to relieve respiratory muscles of their work, and to protect the usually obtunded patient's airways.

However, mechanical ventilation may constitute a risk factor for the development, or the worsening, of ARDS.

Aside from the infectious complications arising from invasive ventilation with tracheal intubation, positive-pressure ventilation directly alters lung mechanics during ARDS. The result is higher mortality, i.e. through baro-trauma, when these techniques are used.

In 1998, Amato *et al.* published a paper showing substantial improvement in the outcome of patients ventilated with lower tidal volumes ($V_t$) (6 mL·kg$^{-1}$). This result was confirmed in a 2000 study sponsored by the NIH. Although both these studies were widely criticized for several reasons, and although the authors were not the first to experiment lower-volume ventilation, they shed new light on the relationship between mechanical ventilation and ARDS.

One opinion is that the forces applied to the lung by the ventilator may work as a lever to induce further damage to lung parenchyma. It appears that shear stress at the interface between collapsed and aerated units may result in the breakdown of aerated units, which inflate asymmetrically due to the 'stickiness' of surrounding flooded alveoli. The fewer such interfaces around an alveolus, the lesser the stress.

Indeed, even relatively low stress forces may induce signal transduction systems at the cellular level, thus inducing the release of inflammatory mediators.

This form of stress is thought to be applied by the transpulmonary pressure (gradient) ($P_l$) generated by the ventilator or, better, its cyclical variations. The better outcome obtained in patients ventilated with lower $V_t$ may be interpreted as a beneficial effect of the lower $P_l$. Transpulmonary pressure, is an indirect function of the $V_t$ setting on the ventilator, and only trial patients with plateau pressures (a surrogate for the actual $P_l$) were less than 32 $cmH_2O$ (3.1 kPa) had improved survival.

The way $P_l$ is applied on alveolar surface determines the shear stress to which lung units are exposed. ARDS is characterized by a usually inhomogeneous reduction of the airspace, and thus by a tendency towards higher $P_l$ at the same $V_t$, and towards *higher* stress on *less* diseased units.

The inhomogeneity of alveoli at different stages of disease is further increased by the gravitational gradient to which they are exposed, and the different perfusion pressures at which blood flows through them. Finally, abdominal pressure exerts an additional pressure on inferoposterior lung segments, favoring compression and collapse of those units.

The different mechanical properties of alveoli in ARDS may be interpreted as having varying *time constants* (the product of alveolar compliance × resistance). A long time constant indicates an alveolus which opens slowly during tidal inflation, as a consequence of contrasting pressure around it, or altered water-air interface inside it (loss of surfactant, flooding).

Slow alveoli are said to be 'kept open' using positive end-expiratory pressure, a feature of modern ventilators which maintains a positive airway pressure throughout the whole respiratory cycle. A higher mean pressure cycle-wide slows the collapse of diseased units, but it has to be weighed against the corresponding elevation in $P_I$/plateau pressure. Newer ventilatory approaches attempt to maximize mean airway pressure for its ability to 'recruit' collapsed lung units while minimizing the shear stress caused by frequent openings and closings of aerated units.

The prone position also reduces the inhomogeneity in alveolar time constants induced by gravity and edema. If clinically appropriate, mobilization of the ventilated patient can assist in achieving the same goal.

### Progression

If the underlying disease or injurious factor is not removed, the amount of inflammatory mediators released by the lungs in ARDS may result in a systemic inflammatory response syndrome (or sepsis if there is lung infection). The evolution towards shock and/or multiple organ failure follows paths analogous to the pathophysiology of sepsis.

This adds up to the impaired oxygenation which is the central problem of ARDS, as well as to respiratory acidosis, which is often caused by ventilation techniques such as permissive hypercapnia which attempt to limit ventilator-induced lung injury in ARDS.

The result is a critical illness in which the 'endothelial disease' of severe sepsis/SIRS is worsened by the pulmonary dysfunction, which further impairs oxygen delivery.

## *Treatment*

### General

Acute respiratory distress syndrome is usually treated with mechanical ventilation in the Intensive Care Unit. Ventilation is usually delivered through oro-tracheal intubation, or tracheostomy whenever prolonged ventilation (≥2 weeks) is deemed inevitable.

The possibilities of non-invasive ventilation are limited to the very early period of the disease or, better, to prevention in individuals at risk for the development of the disease (atypical pneumonias, pulmonary contusion, major surgery patients).

Treatment of the underlying cause is imperative, as it tends to maintain the ARDS picture.

Appropriate antibiotic therapy must be administered as soon as microbiological culture results are available. Empirical therapy *may* be appropriate if local microbiological surveillance is efficient. More than 60% ARDS patients experience a (nosocomial) pulmonary infection either before or after the onset of lung injury.

The origin of infection, when surgically treatable, must be operated on. When sepsis is diagnosed, appropriate local protocols should be enacted.

Commonly used supportive therapy includes particular techniques of mechanical ventilation and pharmacological agents whose effectiveness with respect to the outcome has not yet been proven. It is now debated whether mechanical ventilation is to be considered mere supportive therapy or actual treatment, since it may substantially affect survival.

## Mechanical ventilation

The overall goal is to maintain acceptable gas exchange and to minimize adverse effects in its application. Three parameters are used: PEEP (positive end-expiratory pressure, to maintain maximal recruitment of alveolar units), mean airway pressure (to promote recruitment and predictor of hemodynamic effects) and plateau pressure (best predictor of alveolar overdistention).

Conventional therapy aimed at tidal volumes ($V_t$) of 12-15 ml/kg. Recent studies have shown that high tidal volumes can overstretch alveoli resulting in volutrauma (secondary lung injury). The ARDS Clinical Network, or ARDSNet, completed a landmark trial that showed improved mortality when ventilated with a tidal volume of 6 ml/kg compared to the traditional 12 ml/kg. Low tidal volumes ($V_t$) may cause hypercapnia and atelectasis due to their inherent tendency to increase dead space.

Low tidal volume ventilation was the primary independent variable associated with reduced mortality in the NIH-sponsored ARDSnet trial of tidal volume in ARDS. Plateau pressure less than 30 cm $H_2O$ was a secondary goal, and subsequent analyses of the data from the ARDSnet trial (as well as other experimental data) demonstrate that there appears to be NO safe upper limit to plateau pressure; that is, regardless of plateau pressure, patients fare better with low tidal volumes.

## APRV (Airway Pressure Release Ventilation) and ARDS / ALI

No particular ventilator mode is known to improve mortality in ARDS. The landmark ARDSNet trial used a volume controlled mode and showed decreased mortality with smaller volumes. However, other modes of ventilation have not been directly compared to volume controlled ventilation.

Some practitioners favor airway pressure release ventilation (APRV). Advantages to APRV ventilation are alleged to include: decreased airway pressures, decreased minute ventilation, decreased dead-space ventilation, promotion of spontaneous breathing, almost 24 hour a day alveolar recruitment, decreased use of sedation, near elimination of neuromuscular blockade, optimized arterial blood gas results, mechanical restoration of FRC (functional residual capacity), a positive effect on cardiac output (due to the negative inflection from the elevated baseline with each spontaneous breath), increased

organ and tissue perfusion, potential for increased urine output secondary to increased renal perfusion.

None of these putative advantages have been shown to translate to better outcomes for patients with ARDS in large, randomized, multicenter trials

The main disadvantage of APRV is that it is in some ways exactly opposite of the low tidal volume ventilation strategy that was demonstrated to be effective in the ARDSNet trial. In that trial, a strategy of low tidal volumes was found to be beneficial compared to high tidal volumes. APRV is, in essence, low frequency, very high volume ventilation. All theoretical justifications pale in comparison to data that suggest that low alveolar pressures and hence low volumes benefit patients with ARDS.

A study is needed to evaluate whether APRV will reduce patient mortality when compared to the ARDSNet protocol.

## Positive end-expiratory pressure

Positive end-expiratory pressure (PEEP) is used in mechanically-ventilated patients with ARDS to improve oxygenation. In ARDS, three populations of alveoli can be distinguished. There are normal alveoli which are always inflated and engaging in gas exchange, flooded alveoli which can never, under any ventilatory regime, be used for gas enchange, and atelectatic or partially flooded alveoli that can be "recruited" to participate in gas exchange under certain ventilatory regimes. The recruitable aveoli represent a continuous population, some of which can be recruited with minimal PEEP, and others which can only be recruited with high levels of PEEP. An additional complication is that some or perhaps most alveoli can only be opened with higher airway pressures than are needed to keep them open. Hence the justification for maneuvers where PEEP is increased to very high levels for seconds to minutes before dropping the PEEP to a lower level. Finally, PEEP can be harmful. High PEEP necessarily increases mean airway pressure and alveolar pressure. This in turn can damage normal alveoli by overdistension resulting in DAD.

The 'best PEEP' used to be defined as 'some' $cmH_2O$ above the lower inflection point (LIP) in the sigmoidal pressure-volume relationship curve of the lung. Recent research has shown that the LIP-point pressure is no better than any pressure above it, as recruitment of collapsed alveoli, and more importantly the overdistension of aerated units, occur throughout the whole inflation. Despite the awkwardness of most procedures used to trace the pressure-volume curve, it is still used by some to define the *minimum* PEEP to be applied to their patients. Some of the newest ventilators have the ability to automatically plot a pressure-volume curve. The possibility of having an 'instantaneous' tracing trigger might produce renewed interest in this analysis.

PEEP may also be set empirically. Some authors suggest performing a 'recruiting maneuver' (i.e., a short time at a very high continuous positive airway pressure, such as 50 $cmH_2O$ (4.9 kPa), to recruit, or open, collapsed units with a high distending pressure)

before restoring previous ventilation. The final PEEP level should be the one just before the drop in $PaO_2$ (or peripheral blood oxygen saturation) during a step-down trial.

Intrinsic PEEP (iPEEP), or auto-PEEP, first described by John Marini of St. Paul Regions Hospital, is a potentially unrecognized contributor to PEEP in patients. When ventilating at high frequencies, its contribution can be substantial, particularly in patients with obstructive lung disease. iPEEP has been measured in very few formal studies on ventilation in ARDS patients, and its contribution is largely unknown. Its measurement is recommended in the treatment of ARDS patients, especially when using high-frequency (oscillatory/jet) ventilation.

A compromise between the beneficial and adverse effects of PEEP is inevitable.

## Prone position

Distribution of lung infiltrates in acute respiratory distress syndrome is non-uniform. Repositioning into the prone position (face down) might improve oxygenation by relieving atelectasis and improving perfusion. However, although the hypoxemia is overcome there seems to be no effect on overall survival.

## Fluid management

Several studies have shown that pulmonary function and outcome are better in patients that lost weight or pulmonary wedge pressure was lowered by diuresis or fluid restriction.

## Corticosteroids

A Meduri et al. study has found significant improvement in ARDS using modest doses of corticosteroids. The initial regimen consists of methylprednisolone 2 mg/kg daily. After 3–5 days a response must be apparent. In 1–2 weeks the dose can be tapered to methylprednisolone 0.5-1.0 mg daily. Patients with ARDS do not benefit from high-dose corticosteroids. This was a study involving a small number of patients in one center. A recent NIH-sponsored multicenter ARDSnet LAZARUS study of corticosteroids for ARDS demonstrated that they are not efficacious in ARDS.

## Nitric oxide

Inhaled nitric oxide (NO) potentially acts as selective pulmonary vasodilator. Rapid binding to hemoglobin prevents systemic effects. It should increase perfusion of better ventilated areas. There are no large studies demonstrating positive results. Therefore its use must be considered individually.

Almitrine bismesylate stimulates chemoreceptors in carotic and aortic bodies. It has been used to potentiate the effect of NO, presumably by potentiating hypoxia-induced pulmonary vasoconstriction. In case of ARDS it is not known whether this combination is useful.

### Surfactant therapy

To date no prospective controlled clinical trial has shown a significant mortality benefit of exogenous surfactant in ARDS.

## *Complications*

Since ARDS is an extremely serious condition which requires invasive forms of therapy it is not without risk. Complications to be considered are:

- Pulmonary: barotrauma (volutrauma), pulmonary embolism (PE), pulmonary fibrosis, ventilator-associated pneumonia (VAP).
- Gastrointestinal: hemorrhage (ulcer), dysmotility, pneumoperitoneum, bacterial translocation.
- Cardiac: arrhythmias, myocardial dysfunction.
- Renal: acute renal failure (ARF), positive fluid balance.
- Mechanical: vascular injury, pneumothorax (by placing pulmonary artery catheter), tracheal injury/stenosis (result of intubation and/or irritation by endotracheal tube.
- Nutritional: malnutrition (catabolic state), electrolyte deficiency.

## *Epidemiology*

The annual incidence of ARDS is 1.5–13.5 people per 100,000 in the general population. Its incidence in the intensive care unit (ICU), mechanically ventilated population is much higher. Brun-Buisson *et al.* (2004) reported a prevalence of acute lung injury (ALI) of 16.1% percent in ventilated patients admitted for more than 4 hours. More than half these patients may develop ARDS.

Mechanical ventilation, sepsis, pneumonia, shock, aspiration, trauma (especially pulmonary contusion), major surgery, massive transfusions, smoke inhalation, drug reaction or overdose, fat emboli and reperfusion pulmonary edema after lung transplantation or pulmonary embolectomy may all trigger ARDS. Pneumonia and sepsis are the most common triggers, and pneumonia is present in up to 60% of patients. Pneumonia and sepsis may be either causes or complications of ARDS.

Elevated abdominal pressure of any cause is also probably a risk factor for the development of ARDS, particularly during mechanical ventilation.

The mortality rate varies from 30% to 85%. Usually, randomized controlled trials in the literature show lower death rates, both in control and treatment patients. This is thought to be due to stricter enrollment criteria. Observational studies generally report 50%–60% mortality.

# Chapter 3

# Benzodiazepine Withdrawal Syndrome

## Benzodiazepine withdrawal syndrome

**ICD-10** F13..3

**Benzodiazepine withdrawal syndrome**—often abbreviated to **benzo withdrawal**—is the cluster of symptoms which appear when a person who has taken benzodiazepines long term and has developed benzodiazepine dependence, stops taking benzodiazepine drug(s) or during dosage reductions. Benzodiazepine withdrawal is similar to alcohol withdrawal syndrome and barbiturate withdrawal syndrome and can in severe cases provoke life threatening withdrawal symptoms such as seizures. Severe and life threatening symptoms are mostly limited to abrupt or over-rapid dosage reduction from high doses. A protracted withdrawal syndrome may develop in a proportion of individuals with symptoms such as anxiety, irritability, insomnia and sensory disturbances. In a small number of people it can be severe and resemble serious psychiatric and medical conditions such as schizophrenia and seizure disorders. A serious side effect of benzodiazepine withdrawal is suicide.

The protracted withdrawal can be minimised in intensity and severity by a slow gradual reduction in dosage. Withdrawal of benzodiazepines is usually beneficial due to the adverse effects associated with the long-term use of benzodiazepines. However, it has been recommended that long-term users of benzodiazepines not be forced to withdraw against their will.

Chronic exposure to benzodiazepines causes physical adaptations in the brain that counteract the drug's effects. This is known as a tolerance and physical dependence. When the drug is removed or dosage reduced in an individual physically dependent on benzodiazepines, numerous withdrawal symptoms both physical and psychological may appear and will remain present until the body reverses the physical dependence by making adaptions to the drug-free environment and thus returning the brain to normal function. Generally, the higher the dose and the longer a benzodiazepine is used and the more rapidly a benzodiazepine is discontinued, the more likely severe withdrawal symptoms will occur. However, severe withdrawal symptoms can still occur during gradual dose reduction or from relatively low doses.

In certain selected patient groups the occurrence of withdrawal symptoms is as high as 100%, whereas in unselected patient groups more than 50% of subjects are able to discontinue benzodiazepines with mild or even no withdrawal symptoms at all. Withdrawal symptoms may persist for weeks or months after cessation of benzodiazepines. In a smaller subset of patients withdrawal symptoms may continue at a sub acute level for many months or even a year or more. Long term use of benzodiazepines may lead to withdrawal like symptoms emerging despite a constant therapeutic dose. Correctly attributing previously misdiagnosed withdrawal symptoms such as anxiety to the withdrawal effects of benzodiazepines, individualised taper strategies according to withdrawal severity, the addition of alternative strategies such as reassurance and referral to benzodiazepine withdrawal support groups increase the success rate of withdrawal. Withdrawal symptoms can resemble psychiatric symptoms which doctors often interpret as evidence for the need of benzodiazepines which in turn leads to withdrawal failure and reinstatement of benzodiazepines, often to higher doses.

## *Background*

Sedative hypnotics, such as benzodiazepines, barbiturates and alcohol cause the most serious medical complications during withdrawal. They are considered more clinically hazardous to withdraw from than opiates. Inappropriate long-term use of benzodiazepines by patients is common. Due to tolerance and physical and psychological dependence, benzodiazepines are generally recommended only for short-term use, several weeks, followed by a dose titration off of the medication. The over-prescribing of benzodiazepines on a long-term basis can cause dependence and have many adverse effects on health. Patients typically receive little advice and support from their doctors. As long-term treatment even using low doses of benzodiazepines is associated with adverse effects such as cognitive impairments, withdrawal from benzodiazepines is advised.

Many patients wish to withdraw from benzodiazepines owing to concerns of adverse effects from prolonged use and many people have successfully withdrawn from the drugs worldwide. As a result benzodiazepine dependency and withdrawal have been extensively researched in the medical literature. A summary of the medical literature on benzodiazepines and techniques for withdrawal, combined with the clinical expertise of Professor Heather Ashton in psychopharmacology, psychiatry and the running of a withdrawal clinic for 12 years, has led to a well-known patient's guide:The Ashton Manual. With sufficient motivation and the proper approach, almost all patients can successfully withdraw from benzodiazepines. However, long term users who are dependent on benzodiazepines must not be made to stop abruptly, as they are at high risk of a severe and possibly life threatening withdrawal syndrome. A slower withdrawal rate with a gradually tapered dose typically mitigates this risk.

## *Signs and symptoms*

Some of the withdrawal symptoms are identical to the symptoms for which the medication was originally prescribed. The ability to determine the difference between

relapse and rebound is very important during the withdrawal phase and can often lead to a misdiagnosis. Withdrawal symptoms from low dose dependence typically last 6–12 months and gradually improve over that time period. Symptoms may lack a psychological cause and can fluctuate in intensity with periods of good and bad days until eventual recovery. For this reason, many experts agree that after withdrawal from long term or even fairly short term use of benzodiazepine drugs, at least six months should have elapsed prior to re-evaluating the symptoms and updating a diagnosis.

Withdrawal symptoms can occur while on a stable dose of benzodiazepines due to the "tolerance withdrawal" phenomenon, where the body experiences "withdrawal effects" and craves increasing doses to feel normal which can lead to dosage escalation, but most often withdrawal symptoms occur during dosage reduction. Onset of the withdrawal syndrome from long half-life benzodiazepines might be delayed for up to 3 weeks, although withdrawal symptoms from short-acting benzodiazepines often presents early, usually within 24–48 hours. Withdrawal symptoms from benzodiazepines or opioids occur after infusions are withdrawn are common among pediatric intensive care patients. The risk of this syndrome developing is increased by total duration of infusion treatment and the total dose given.

The acute benzodiazepine withdrawal syndrome generally lasts for about 2 months but clinically significant withdrawal symptoms may persist, although gradually declining, for many months or even several years. The severity and length of the withdrawal syndrome is likely determined by various factors including rate of tapering, length of use of benzodiazepines and dosage size and possibly genetic factors.

Altering reduction speed according to withdrawal symptom severity is the most effective way of reducing the intensity and duration of withdrawal symptoms. Some people may not fully stabilize between dose reductions even when the rate of reduction is slowed down. Such people sometimes simply need to persist with coming off of benzodiazepines as they may not feel better until they have been fully withdrawn from benzodiazepines for a period of time.

Long term use of benzodiazepines causes cognitive, neurological and intellectual impairments. After one year of abstinence from benzodiazepines cognitive, neurological and intellectual impairments had returned to normal.

Patients who are physically dependent on short-acting anxiolytic benzodiazepines may experience what is known as interdose withdrawal. Interdose withdrawal are withdrawal symptoms which occur between doses when the previous dose wears off. This can lead to symptoms such as rebound anxiety between doses and craving for the next dose of short-acting benzodiazepine.

Symptoms such as rebound insomnia and rebound anxiety may occur after only 7 days administration of benzodiazepines. Another trial demonstrated rebound withdrawal effects after only 18 nights use of lorazepam as a benzodiazepine hypnotic. Rebound day time anxiety and tension develops after only 7 days use of short-acting benzodiazepine

hypnotics. On withdrawal of benzodiazepines after 7 nights use, withdrawal related insomnia rebounds worse than baseline. Intermittent use of benzodiazepines even over a short period of time can cause rebound insomnia. Use of short-acting hypnotics while being effective at initiating sleep worsen the second half of sleep due to withdrawal effects. Day time withdrawal symptoms are commonly associated with triazolam. This is due to its very short half life. After only 10 nights of triazolam use patients report anxiety, distress, weight loss, panics and depression, derealization, and develop paranoia. These reactions occurred more commonly with triazolam than lormetazepam which has an intermediate half life. Thus the more short acting a benzodiazepine hypnotic the more severe the day time withdrawal symptoms. Day time withdrawal related anxiety can also occur from chronic nightly nonbenzodiazepine hypnotic usage such as with zopiclone. After only 8–9 weeks of alprazolam (Xanax) taken at a fixed prescribed dose, the following symptoms have been found to occur during abrupt discontinuation: dysphoria, fatigue, low energy, confusion, and elevated systolic blood pressure, severe anxiety.

**The following symptoms may emerge during gradual dosage reduction but can usually be reduced in intensity or eliminated altogether by reducing the rate of reduction:**

- Anxiety, possible terror and panic attacks
- Agitation and restlessness
- Hypochondriasis
- Dilated pupils
- Impaired concentration
- Nightmares
- Insomnia
- Muscular spasms, cramps or fasciculations
- Electric shock sensations
- Blurred vision
- Dizziness
- Dry mouth
- Aches and pains
- Hearing impairment
- Taste and smell disturbances
- Chest pain
- Flu like symptoms
- Impaired memory and concentration
- Increased sensitivity to touch
- Increased sensitivity to sound
- Sounds louder than usual
- Objects moving
- Increased urinary frequency
- Numbness and tingling
- Hot and cold flushes
- Headache
- Rebound REM sleep

- Stiffness
- Fatigue and weakness
- Hyperosmia
- Restless legs syndrome
- Metallic taste
- Photophobia
- Paranoia
- Hypnagogia-hallucinations
- Nausea and vomiting
- Elevation in blood pressure
- Tachycardia
- Hypertension
- Postural hypotension
- Depression (can be severe), possible suicidal ideation
- Tremor
- Perspiration
- Loss of appetite and weight loss
- Dysphoria
- Depersonalization
- Derealisation (Feelings of unreality)
- Obsessive compulsive disorder
- Tinnitus
- Paraesthesia
- Visual disturbances
- Mood swings
- Indecision
- Gastrointestinal problems (Irritable bowel syndrome)

**An abrupt or over-rapid discontinuation of benzodiazepines may result in a more serious and very unpleasant withdrawal syndrome that may additionally result in:**

- Convulsions, which may result in death
- Catatonia, which may result in death
- Coma (rare)
- Suicide
- Attempted suicide
- Suicidal ideation
- Self harm
- Hyperthermia
- Delusions
- Homicide ideations
- Urges to shout, throw, break things or to harm someone
- Violence
- Post Traumatic Stress Disorder
- Organic brain syndrome
- Psychosis

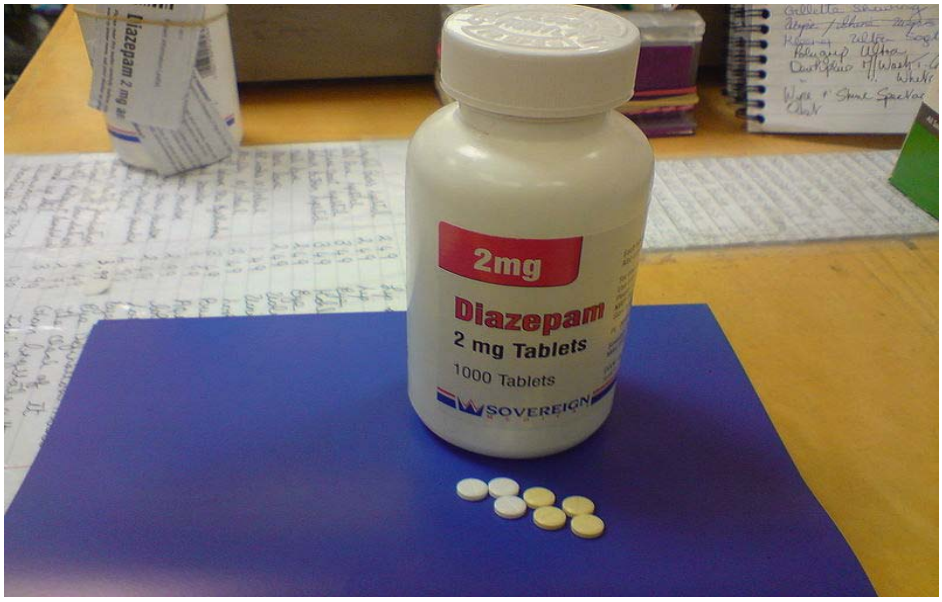
- Confusion
- Mania
- Neuroleptic malignant syndrome like event (rare)
- Delirium tremens

As withdrawal progresses patients often find that their physical and mental health improves with improved mood and improved cognition.

## *Mechanism and pathophysiology*

Benzodiazepines cause enhanced GABA inhibition; when this inhibition is sustained, i.e. long-term use, this increased central nervous system depression is balanced by neuroadaptations which result in decreased GABA inhibition and increased excitability of the glutamate system. When benzodiazepines are stopped, these neuroadaptations are "unmasked" leading to excitability of the nervous system and the appearance of withdrawal symptoms. Increased glutamate excitatory activity during withdrawal is believed to result in kindling phenomena. It has been found that those who have a prior history of withdrawing from benzodiazepines are less likely to succeed the next time around. Repeated benzodiazepines withdrawals, like with alcohol withdrawal, may lead to sensitization or kindling of the CNS, possibly leading to worsening cognition and symptomatology and making each subsequent withdrawal period worse.

## *Management*




Diazepam 2 mg and 5 mg diazepam tablets, which are commonly used in the treatment of benzodiazepine withdrawal.


Chlordiazepoxide 5 mg capsules, which are sometimes used as an alternative to diazepam for benzodiazepine withdrawal. Like diazepam it has a long elimination half life and long acting active metabolites.

The success rate of a slow withdrawal schedule is approximately 65%, however, some studies have found higher success rates of between 88 – 100 percent. Studies have shown that psychiatric patients have a similar success rate of staying off benzodiazepines after a slow withdrawal schedule at 2 year followup post withdrawal. Withdrawal from benzodiazepines does not lead to an increased switching over to antidepressants. The slower the withdrawal rate the less intense the withdrawal symptoms and there is strong anecdotal evidence that slower withdrawal rates decrease the risk of developing a severe protracted benzodiazepine withdrawal syndrome. The rate of withdrawal preferably utilising either diazepam, chlordiazepoxide, for their long half lifes and low potency dose forms, is best carried out according to the withdrawing patient's body response to dose cuts. The British National Formulary, a medical guidance book which is issued to all British doctors, states that it is better to withdraw too slowly rather than too quickly from benzodiazepines.

## Medications and interactions

Fluoroquinolone antibiotics have been noted by Professor Heather Ashton and confirmed in a study as often causing serious complications in patients chronically taking benzodiazepines or undergoing withdrawal from benzodiazepines. This is probably the result of the GABA antagonistic effect of fluoroquinolones. Fluoroquinolones have also been found to competitively displace benzodiazepines from benzodiazepine receptors which can precipitate acute withdrawal symptoms in benzodiazepine dependent subjects. A study reported higher than usual CNS toxicity from fluoroquinolones in subjects who

were dependent on or in withdrawal from benzodiazepines. Of the general public 1 – 4% of the public will experience CNS toxicity from fluoroquinolones which may be severe. The incidence of severe CNS toxicity occurs significantly more frequently in the benzodiazepine dependent population. The CNS adverse reactions from fluoroquinolones were similar to those seen in benzodiazepine withdrawal and persisted for weeks or months before subsiding. The symptoms included depression, anxiety, psychosis, paranoia, severe insomnia, parathesia, tinnitus, hypersensitivity to light and sound, tremors, status epilepticus, suicidal thoughts and suicide attempt. The study confirmed that fluoroquinolone CNS toxicity can be serious, occurs more frequently in benzodiazepine dependent subjects and concluded that fluoroquinolone antibiotics should be contraindicated in patients who are dependent on or in benzodiazepine withdrawal. A person with an already compromised GABA system (for example, one going through benzodiazepine withdrawal) is likely to be at an even greater risk of severe adverse reactions. NSAIDs have some mild GABA antagonistic properties and some may even displace benzodiazepines from their binding site according to animal research. They do not cause as potent antagonism of GABA function as fluoroquinolones. However, NSAIDs taken in combination with fluoroquinolones cause a very significant increase in GABA antagonism which may result in very severe GABA antagonism, GABA toxicity, and seizures and other severe adverse effects.

Benzodiazepine withdrawal related psychosis is generally unresponsive to antipsychotic agents. Antipsychotics should be avoided during benzodiazepine withdrawal as they tend to aggravate withdrawal symptoms, including convulsions. Some antipsychotic agents may be more risky during withdrawal than others, especially clozapine, olanzapine or low potency phenothiazines (e.g., chlorpromazine), as they lower the seizure threshold and can worsen withdrawal effects; if used, extreme caution is required.

Buproprion, which is used primarily as an antidepressant and smoking cessation aid, is contraindicated in persons experiencing abrupt withdrawal from benzodiazepines or other sedative-hypnotics (e.g. alcohol), due to an increased risk of seizures. The addition of an SSRI antidepressant has been found to have little value in the treatment of benzodiazepine withdrawal. Similarly, the addition of progesterone has been found to be ineffective for managing benzodiazepine withdrawal.

Avoidance of or reduction in caffeine intake is sometimes recommended due to reports of it worsening withdrawal symptoms and its stimulatory properties. Interestingly, at least one animal study has shown some modulation of the benzodiazepine site by caffeine which produces a lowering of seizure threshold.

Once the benzodiazepine addicted or physically dependent individual has successfully withdrawn from benzodiazepines, they should avoid taking even occasionally benzodiazepines or cross tolerant drugs such as alcohol, barbiturates or the nonbenzodiazepines Z drugs, which all have a similar mechanism of action, for at least four months and as long as two years, depending on personal biochemistry. This is because tolerance to benzodiazepines has been demonstrated to be still present in patients who have discontinued benzodiazepines between four months and two years post

withdrawal. In these patients, even once off low dose, re-exposures to benzodiazepines typically resulted in a reactivation of the tolerance and benzodiazepine withdrawal syndrome. Alcohol, even mild to moderate use, has been found to be a significant predictor of withdrawal failure, probably because of its cross tolerance with benzodiazepines.

## Withdrawal process

Detoxification of a benzodiazepine dependent individual is often carried out using an equivalent dose of either diazepam or chlordiazepoxide to the benzodiazepine the individual is dependent on and by reducing in steps of 10% every 2–4 weeks depending on the severity of the dependency and the patient's response to reductions. However, if withdrawal is carried out slow enough and preferably using an equivalent dose of diazepam or chlordiazepoxide to withdraw, many benzodiazepine dependent patients find that they experience little or sometimes no withdrawal when it comes time to come off the last 0.5 mg dose of diazepam or 5 mg dose of chlordiazepoxide. Those who have withdrawn slow enough but still experience withdrawal effects typically find that their withdrawal symptoms have largely disappeared after a few months. It is important to note that the elimination half life of diazepam and chlordiazepoxide as well as other long half-life benzodiazepines is twice as long in the elderly compared to younger individuals. Many doctors do not adjust benzodiazepine dosage according to age in elderly patients.

It is strongly recommended that during benzodiazepine withdrawal that the drug used is diazepam (Valium) or chlordiazepoxide (Librium) as they are available in low potency doses in addition to having a longer half-life than most other benzodiazepines such as lorazepam (Ativan) or alprazolam (Xanax) and hence a smoother withdrawal. It can be very difficult to withdraw successfully if the addiction is to a short to intermediate half-life benzodiazepine such as temazepam (Normison), lorazepam (Ativan) or alprazolam (Xanax), as the intensity of the withdrawal syndrome can be too high and debilitating.

Failure to use the correct benzodiazepine equivalencies when switching benzodiazepines either therapeutically or in the management of withdrawal may produce severe withdrawal reactions. This was illustrated in a case reported in the medical literature of a man who had been taking doses of lorazepam and alprazolam equivalent of 60 mg of diazepam. He was then switched from the lorazepam and alprazolam to only 7 mg of diazepam per day. Within 36 hours the patient developed somatic symptoms and became convinced that he had an underlying pathology and impulsively attempted suicide by stabbing himself in the abdomen causing himself serious injury requiring emergency surgery. His symptoms and suicide attempt were diagnosed by his GP and psychiatrist as benzodiazepine withdrawal. The patient again tried to withdraw from benzodiazepines but did so too rapidly with erratic dosage reductions and again attempted suicide by inflicting serious stab wounds to his neck and chest which resulted in admittance to a psychiatric unit. The author warned that self harm can be a feature of benzodiazepine withdrawal.

## Controversy

In some instances, a "detox" or other inpatient facility will take a person off a benzodiazepine "cold turkey" — replacing it with a short 1 – 2 week taper of phenobarbital (a barbiturate) to prevent seizures. Most physicians and medical authorities agree that in the majority of cases a slow taper is preferred to a rapid taper or "cold turkey" withdrawal from a benzodiazepine. A less harsh method is replacement with phenobarbital followed by a slow reduction of the phenobarbital. In a comparison study a rapid detoxification using benzodiazepines was found to be superior to a phenobarbital rapid detoxification. Often individuals dependent on benzodiazepines are judged to be "an addict" when presenting to their doctor with withdrawal symptoms and inappropriately referred to a substance abuse center. Such referrals are only appropriate for substance abusers and not for non-abusers who are physically dependent on benzodiazepines.

Detoxification from benzodiazepines can be very problematic due to the extremely prolonged and severe withdrawal symptoms that it can provoke. This can lead to collapse of marriages, business failures, bankruptcy, committal to hospital and the most serious adverse effect which is suicide. The success rate of abrupt or over-rapid withdrawal is quite low with high numbers of drop outs and failures. With a slow gradual withdrawal program the success rate is between 88 – 100 percent.

Over-rapid withdrawal and lack of explanation and failure to reassure individuals that what they are experiencing is withdrawal symptoms and is temporary have led some people to experience increased panic and fears that they are going mad, with some people developing a condition similar to Post Traumatic Stress Disorder as a result. A slow withdrawal regime coupled with reassurance seems to improve the outcome for individuals undergoing benzodiazepine withdrawal.

More recent research is showing promise with the use of flumazenil in the management of benzodiazepine detoxification. Flumazenil has been found to stimulate the reversal of tolerance and the normalization of receptor function. However, further research is needed in the form of randomised trials to demonstrate its role in the treatment of benzdiazepine withdrawal. Flumazenil stimulates the up-regulation and reverses the uncoupling of benzodiazepine receptors to the $GABA_A$ receptor thereby reversing tolerance and reducing withdrawal symptoms and relapse rates. Due to only limited research and experience and possible risks involved the flumazenil detoxification method is controversial and can only be done as an inpatient procedure under medical supervision.

A further drug called imidazenil has received some research for management of benzodiazepine withdrawal but is not currently used in the treatment of benzodiazepine withdrawal. Carbamazepine, an anticonvulsant was found to be ineffective in preventing status epilepticus from occurring during clonazepam withdrawal in two patients who were taking clonazepam as an anti epileptic agent for pre-existing seizure disorder.

## *Prognosis*

Benzodiazepine dependence is a potentially clinically serious condition and its withdrawal syndrome is complex and often protracted in time course. Patients often have persisting withdrawal symptoms for 6 months to a year or more. Symptoms can include anxiety, irritability, insomnia and an increased sensitivity to light and sound. A small number of people withdrawing from benzodiazepines experience a severe protracted withdrawal syndrome which can include symptoms such as paresthesias, psychosis. These symptoms occur despite no pre-existing history of these symptoms. It is important to distinguish between a return of any pre-existing disorder, a worsening of the pre-existing disorder due to protracted withdrawal and pure protracted withdrawal. Symptoms of protracted withdrawal over time gradually improves whereas symptoms due to other causes typically doesn't improve. Protracted withdrawal syndrome can mimic a range of medical and psychiatric disorders including schizophrenia, agitated depression, generalised anxiety disorder, panic disorder and complex partial seizures. Protracted withdrawal symptoms can be punctuated by periods of good days and bad days. When symptoms increase periodically during protracted withdrawal physiological changes may be present including dilated pupils as well as an increase in blood pressure and heart rate. The change in symptoms has been proposed to be due to changes in receptor sensitivity for GABA during the process of tolerance reversal.

Protracted withdrawal symptoms refers to symptoms persisting for a protracted time, perhaps a year or more. Patients who experience protracted withdrawal from benzodiazepines, which more commonly occurs from over-rapid withdrawal, can be reassured that the evidence shows that symptoms do continue to fade and return to normal over a period of many months or several years. A figure of 10–15% of patients withdrawing from benzodiazepines may experience a protracted withdrawal syndrome. There is evidence that a slow-withdrawal rate significantly reduces the risk of a protracted and/or severe withdrawal state. There is no known cure for protracted benzodiazepine withdrawal syndrome except time. The post withdrawal syndrome may linger for many months in 10–15% of people and for a smaller number of unfortunate patients for several years. Studies following people up beyond the initial acute withdrawal stage have shown that for many patients symptoms continue to improve the longer they stay off the drug, often to the point where they can eventually resume their normal lives even after years of incapacity imposed by chronic benzodiazepines.

The causes of persisting benzodiazepine withdrawal symptoms are a combination of pharmacological factors such as persisting drug induced receptor changes, psychological factors both caused by the drug and separate from the drug and possibly in some cases, particularly high dose users structural brain damage or structural neuronal damage.

Sensory withdrawal related disturbances which can be acute or protracted in duration and are among the clinical features of the benzodiazepine withdrawal syndrome. Protracted tinnitus has been found to be a complication of discontinuation of benzodiazepines with tinnitus persisting for many months or up to a year or more after discontinuation of therapeutic doses of benzodiazepines. Appearance of the tinnitus occurs during dose

reduction or discontinuation of benzodiazepines and is alleviated by recommencement of benzodiazepines.

A clinical trial of patients taking the benzodiazepine alprazolam (Xanax) for as little as 8 weeks triggered protracted symptoms of memory deficits which were still present after up to 8 weeks post cessation of alprazolam.

A meta-analysis found that the literature shows that cognitive impairments due to benzodiazepine use shows improvements after 6 months after withdrawal but the remaining cognitive impairments may be permanent or may require more than 6 months to reverse.

Neuropsychological testing of a group of patients with persistent benzodiazepine withdrawal symptoms found that psychophysiological markers differed from normal anxiety markers. The study of the group of patients concluded that protracted withdrawal symptoms were a genuine iatrogenic condition caused by the long term prescription of benzodiazepines.

Hoffmann–La Roche pharmaceutical company, the inventor of both the first few, as well as most benzodiazepines, such as Librium (chlordiazepoxide), Valium (diazepam), Rohypnol (flunitrazepam), Dormicum (midazolam) and Klonopin/Rivotril (clonazepam), in a 2007 product information publication, acknowledges the existence of protracted benzodiazepine withdrawal syndromes and recommends that its product flumazenil is not used to treat protracted benzodiazepine withdrawal syndromes.

## Examples

Some common protracted withdrawal symptoms include: cognitive deficits, gastrointestinal complaints, insomnia, tinnitus, paraesthesiae (tingling and numbness), pain (usually in limbs and extremities), muscle pain, weakness, tension, painful tremor, shaking attacks, jerks, and blepharospasm.

## Effect of flumazenil

A study into the effects of the benzodiazepine receptor antagonist, flumazenil, on benzodiazepine withdrawal symptoms persisting after withdrawal was carried out by Lader and Morton. Study subjects had been benzodiazepine-free for between one month and five years, but all reported persisting withdrawal effects to varying degrees. Persistent symptoms included clouded thinking, tiredness, muscular symptoms such as neck tension, depersonalisation, cramps and shaking and the characteristic perceptual symptoms of benzodiazepine withdrawal, namely, pins and needles, burning skin, pain and subjective sensations of bodily distortion. Therapy with 0.2–2 mg of flumazenil intravenously was found to decrease these symptoms in a placebo controlled study. This is of interest as benzodiazepine receptor antagonists are neutral and have no clinical effects. The author of the study suggested that the most likely explanation is that past benzodiazepine use and subsequent tolerance had locked the conformation of the GABA-

BZD receptor complex into an inverse agonist conformation, and that the antagonist flumazenil resets benzodiazepine receptors to their original sensitivity. Flumazenil was found in this study to be a successful treatment for protracted benzodiazepine withdrawal syndrome, but it was noted that further research is required. A study by Professor Borg in Sweden produced similar results in patients suffering from protracted withdrawal, due the dearth of studies on the subject.

## *In the elderly*

A study of the elderly who were benzodiazepine dependent found that withdrawal could be carried out with few complications and could lead to improvements in sleep and cognitive abilities. At 52 weeks after successful withdrawal a 22% improvement in cognitive status was found as well as improved social functioning. Those that remained on benzodiazepines experienced a 5% decline in cognitive abilities which seemed to be faster than that seen in normal aging suggesting that the longer the intake of benzodiazepines the worse the cognitive effects become. Some worsening of symptoms were seen in the first few months of benzodiazepine abstinence but at 24 week follow up elderly subjects were clearly improved compared to those who remained on benzodiazepines. Improvements in sleep were seen at 24 and 52 week follow up. The authors concluded that benzodiazepines were not effective in the long term for sleep problems except in suppressing withdrawal related rebound insomnia. Improvements were seen between 24 and 52 weeks post withdrawal in many factors including improved sleep and improvements in several cognitive and performance abilities. There were some cognitive abilities which did not improve which are sensitive to benzodiazepines as well as age such as episodic memory. The authors however cited a study in younger patients who at 3.5 year follow-up showed no memory impairments and speculated that certain memory functions take longer to recover from chronic benzodiazepine use and that further improvements in elderly peoples cognitive function may occur beyond 52 weeks post withdrawal. The reason that it took 24 weeks for improvements to be seen after cessation of benzodiazepine use was due to the time it takes the brain to adapt to the benzodiazepine free environment. At 24 weeks significant improvements were found including accuracy of information processing improved but a decline was seen in those who remained on benzodiazepines. Further improvements were noted at 52 week follow-up indicating ongoing improvements with benzodiazepine abstinence. Younger people on benzodiazepines also experience cognitive deterioration in visual spacial memory but are not as vulnerable as the elderly to the cognitive effects of benzodiazepines. Improved reactions time were noted at 52 weeks in elderly patients free from benzodiazepines. This is an important function in the elderly especially if they drive a car due to the increased risk of road traffic accidents in benzodiazepine users. At 24 week follow up it was found that 80% of people had successfully withdrawn from benzodiazepines. Part of the success was attributed to the placebo method used for part of the trial which broke the psychological dependence on benzodiazepines when the elderly patients realised that they had completed their gradual reduction several weeks previously and had only been taking placebo tablets. This helped reassure them that they could sleep without their pills. The authors also warned of the similarities in pharmacology and mechanism of action of the newer nonbenzodiazepine Z drugs.

## *In pregnancy*

### Neonatal withdrawal syndrome

Benzodiazepines, especially when taken during the third trimester can cause a severe benzodiazepine withdrawal syndrome in the neonate with symptoms including hypotonia, and reluctance to suck, to apnoeic spells, cyanosis, and impaired metabolic responses to cold stress and seizures. The neonatal benzodiazepine withdrawal syndrome has been reported to persist from hours to months after birth.

### Withdrawal during pregnancy

Discontinuing benzodiazepines or antidepressants abruptly due to concerns of teratogenic effects of the medications has a high risk of causing serious complications and therefore is not recommended. For example abrupt withdrawal of benzodiazepines or antidepressants has a high risk of causing extreme withdrawal symptoms including suicidal ideation and a severe rebound effect of the underlying mental health disorder if present. This can lead to hospitalisation of the pregnant mother and may potentially lead to suicide attempts and thus potentially the death of the mother and fetus. One study reported that one third of mothers who suddenly discontinued or very rapidly tapered their medications became acutely suicidal due to 'unbearable symptoms'. One woman had a medical abortion as she felt that she could no longer cope and another woman used alcohol in a bid to combat the withdrawal symptoms from benzodiazepines. Spontaneous abortions may also result from abrupt withdrawal of psychotropic medications including benzodiazepines. The study reported that physicians in general are not aware of the severe consequences of abrupt withdrawal of psychotropic medications such as benzodiazepines or antidepressants.

# Chapter 4

# Cerebellopontine Angle Syndrome

| Cerebellopontine angle syndrome | |
|---|---|
| **ICD-9** | 191.6 - Neoplasms of brain: Cerebellum NOS: Cerebellopontine angle |

The cerebellopontine angle is the anatomic space between the cerebellum and the pons. This is a common site for the growth of acoustic neuromas or schwannomas. A distinct neurologic syndrome of deficits occurs due to the anatomic proximity of the cerebellopontine angle to specific cranial nerves.

## *Anatomy*

The cerebellopontine angle is a space filled with spinal fluid.

## *Signs and Symptoms*

Lesions in the area of cerebellopontine angle cause signs and symptoms secondary to compression of nearby cranial nerves, including cranial nerve V, cranial nerve VII, and cranial nerve VIII.

For example, involvement of CN V from a cerebellopontine mass lesion often results in loss of the ipsilateral corneal reflex.

Patients with larger tumours can develop Bruns nystagmus due to compression of the flocculi.

## *Causes*

### Cerebellopontine angle tumors

- Acoustic neuroma/vestibular schwannoma
- Meningioma
- Cerebellar astrocytoma
- Epidermoid

- Glomus jugulare associated with the glossopharyngeal nerve
- Metastases

## *Treatment*

Medical Therapy

Acoustic neuromas are managed in one of the following 3 ways: (1) surgical excision of the tumor, (2) arresting tumor growth using stereotactic radiation therapy, or (3) careful serial observation.

Observation

Simple observation without any therapeutic intervention has been used in the following groups of patients:

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   * Elderly patients
   * Patients with small tumors, especially if their hearing is good
   * Patients with medical conditions that significantly increase the
risk of operation
   * Patients who refuse treatment
   * Patients with a tumor on the side of an only hearing ear or only
seeing eye
         o In a number of series reported to date, the individuals who
are being observed ultimately require therapeutic intervention in
between 15-40%.
         o During an observation period, most (70% or more) patients
who are eligible for hearing conservation surgery initially lost their
eligibility.
         o Telian has analyzed the important variables that should be
evaluated when observation is considered, and these include the
following:2 1) preoperative hearing in both ears, 2) the risk of
immediate hearing loss as a consequence of surgery, 3) the risk of
facial nerve paralysis, 4) the risk of other surgical complications and
their seriousness, 5) the patient's life expectancy, 6) the size of the
tumor, 7) tumor growth rate, and 8) patients with neurofibromatosis
type 2 (NF2) or bilateral tumors.
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Stereotactic radiotherapy

Stereotactic radiotherapy has emerged within the last 20 years as an alternative to microsurgery for selected patients with acoustic neuroma.

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   * Stereotactic radiation therapy makes use of one of several
radiation sources and is administered using a variety of different
machines with proprietary names (eg, Gamma Knife, CyberKnife,
BrainLAB).
   * Stereotactic therapy uses radiation delivered to a precise point
or series of points to maximize the amount of radiation delivered to
target tissues while minimizing the exposure of adjacent normal
tissues. It can be delivered as a single dose or as multiple
fractionated doses.
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* The effects of radiation delivered at the current low dose likely prevents further tumor growth by causing obliterative endarteritis of the vessels supplying the tumor. Radiosurgery may affect tumor cells undergoing mitosis by causing double strand DNA breaks. Hansen et al demonstrated acoustic neuroma cells are radioresistant at the current low-dose radiation used with radiosurgery.3
* Comparison of microsurgery and stereotactic radiation is difficult for the following reasons:
    - Tumor size is inconsistently reported in the literature.
    - Data using the lower radiation dosages are available for only the past 10 years.
    - Because the goal of radiotherapy is control of tumor growth, understanding whether posttreatment neuroimaging reflects adequate treatment or merely the natural history of vestibular schwannomas is difficult.
    - No data concerning the risk for secondary tumor induction by radiotherapy are available.
* Advantages of radiation therapy include the following:
    - Decreased length of stay
    - Decreased cost
    - Rapid return to full employment
    - Lower immediate posttreatment morbidity and mortality
* Disadvantages of stereotactic radiation include the following:
    - Necessity for regular monitoring and frequent rescanning (In the end, costs associated with long-term monitoring could exceed those of surgery.)
    - Does not eliminate the tumor and may fail to control tumor growth, sometimes requiring salvage surgery.
    - Higher incidence of trigeminal nerve injury.
    - Unknown long-term incidence of secondary malignancies. The best current estimates of developing a secondary malignancy from the radiosurgery are 1 in a 1000 patients over 30 years.
    - Does not address disequilibrium and may lead to long-term balance dysfunction.

## Surgical Therapy

Surgical removal remains the treatment of choice for tumor eradication. Various surgical approaches can be used to remove acoustic tumors. Each approach is discussed in detail in the following sections. Preoperative Details

Three different approaches are used in the management of acoustic neuromas, the retrosigmoid, translabyrinthine, and middle fossa approaches. All have advantages and disadvantages as indicated below.

### Advantages of the retrosigmoid approach

* The retrosigmoid approach can be applied to all acoustic tumors and to many other histologic tumor types. It can be used for operations that sacrifice hearing and operations that attempt to conserve hearing. Its only limitation in this respect is its inapplicability for small tumors that occupy the far-lateral portions of the internal auditory canal.

* The retrosigmoid approach provides the best wide-field visualization of the posterior fossa. The inferior portions of the cerebellopontine angle and the posterior surface of the temporal bone anterior to the porus acusticus are much more clearly observed than via the translabyrinthine approach. Panoramic visualization is especially helpful when displacement of nerves is not predictable, which occurs commonly with meningiomas.
* Hearing conservation surgery can be attempted even for relatively large tumors via the retrosigmoid approach. Destruction of the labyrinth is not required as part of the retrosigmoid approach.

## Disadvantages of the retrosigmoid approach

* The retrosigmoid approach may require cerebellar retraction or resection. Manipulation of the cerebellum provides opportunities for postoperative edema, hematoma, infarction, and bleeding.
* Increased incidence of cerebrospinal fluid leak occurred in some series.
* The retrosigmoid approach is associated with greater likelihood of severe protracted postoperative headache.
* The highest incidence of tumor recurrence or persistence occurs with retrosigmoid approaches.

## Advantages of the translabyrinthine approach

* The translabyrinthine approach provides the best view of the lateral brain stem facing the acoustic tumor.
* Retraction of the cerebellum is almost never necessary.
* The fundus and lateral end of the internal auditory canal are completely exposed; the facial nerve can be identified at a location where it is undistorted by tumor growth and compressed into the labyrinthine segment, decreasing the risk of delayed postoperative facial nerve palsy.
* Incidence of cerebrospinal fluid leak is decreased in some series.
* If the facial nerve has been divided or sacrificed, the translabyrinthine approach may allow restoration of the facial nerve continuity by rerouting the facial nerve and performing a primary anastomosis. Consequently, interposition graft can sometimes be avoided.
* Facial function is more frequently preserved in some series.

## Disadvantages of the translabyrinthine approach

* Hearing sacrifice is complete and unavoidable.
* The inferior portions of the cerebellopontine angle and cranial nerves are not as well visualized as they are in the retrosigmoid approach. The temporal bone anterior to the porus acusticus is also less well visualized.
* A fat graft is required. Removal of fat from the abdomen creates opportunities for donor site complications, including hematoma, bleeding, and infection.
* The sigmoid sinus is more vulnerable to injury. Bleeding from the sigmoid sinus can be difficult to control and can significantly increase operative blood loss. If a dominant sigmoid sinus is occluded

during the operation, postoperative intracranial pressure elevation or venous infarct can occur.
* A high jugular bulb or anteriorly placed sigmoid sinus can substantially compromise the space available for tumor removal. Occasionally, the space is so contracted that another approach has to be selected.

### Advantages of the middle cranial fossa approach

* It is the only procedure that fully exposes the lateral third of the internal auditory canal without sacrificing hearing.
* It is extradural.

### Disadvantages of the middle cranial fossa approach

* The facial nerve generally courses across the anterior superior portion of the tumor. Consequently, it is in the way during tumor removal and is more vulnerable to injury. Although long-term facial nerve outcomes are as good with the middle cranial fossa approach as with other approaches, temporary postoperative paresis is more common.
* The risk of dural laceration and avulsion becomes increasingly more likely as patients become older. The dura mater in elderly patients is more friable. This becomes especially noticeable during the sixth and seventh decades of life.
* The approach provides only very limited exposure of the posterior fossa.
* The operation is technically difficult and demanding.
* Some patients incur postoperative trismus related to manipulation and/or injury to the temporalis muscle.
* The temporal lobe must be retracted, presenting the opportunity for temporal lobe injury, usually in the form of a hematoma that is asymptomatic and, therefore, probably occurs more frequently than is realized. Scattered reports exist of seizure disorder following middle cranial fossa surgery, presumably due to temporal lobe injury.

## Approach Selection

A variety of different considerations go into deciding which approach should be used for any individual patient. These variables are detailed below.

### Preoperative hearing level

If the patient has no useful hearing, either the translabyrinthine or the retrosigmoid approach is selected, depending upon the experience and training of the surgeon. In most centers performing large numbers of surgeries for acoustic tumors, the translabyrinthine approach is preferred. Opinions vary considerably about what constitutes useful hearing. The 50/50 rule is frequently quoted. The rule suggests that individuals with a pure-tone average greater than 50 dB and speech discrimination less than 50% do not have useful or salvageable hearing. Other surgeons have stricter criteria and consider only individuals with better than a 30-dB pure-tone average and more than 70% discrimination for hearing conservation operations.

Auditory brainstem response

Normal preoperative ABR findings favor hearing conservation. Marked abnormalities of ABR wave morphology or increased wave I-III and I-V latencies make hearing conservation less feasible.

Electronystagmography

An abnormal caloric test on electronystagmography (ENG) increases the likelihood of successful hearing conservation surgery. The ENG tests the horizontal semicircular canal, which is innervated by the superior vestibular nerve. A normal ENG finding arguably demonstrates that the superior vestibular nerve is normal. Consequently, the acoustic tumor must have originated from the inferior vestibular nerve, which is directly adjacent to the cochlear nerve. Surgical removal, then, is more likely to directly injure the cochlear nerve or interfere with cochlear blood supply. Vestibular evoked myogenic potential (VEMP) testing is abnormal when the inferior vestibular nerve is affected. As a result, an abnormal VEMP with normal caloric testing on ENG strongly suggests an inferior vestibular nerve tumor with poorer hearing preservation.

Tumor size

Opportunities for hearing conservation decrease as tumors become larger. Hearing is much more difficult to conserve when tumors are 1.5-2.0 cm in diameter than if they are small intracanalicular tumors. Consequently, some surgeons limit hearing conservation surgery to smaller tumors, preferring to use a translabyrinthine approach to maximize the chance of facial nerve conservation for larger tumors.

Tumor position

If hearing conservation is to be attempted and the tumor lies within the lateral portions of the internal auditory canal, many surgeons prefer a middle fossa approach. The middle fossa approach permits direct exposure of the lateral end of the internal auditory canal without sacrificing hearing. The approach is frequently used for any tumor lying completely within the internal auditory canal, although tumors limited to the medial portions of the internal auditory canal can be managed using a retrosigmoid approach. Some surgeons extend the use of the middle fossa technique to include tumors that extend as much as 0.5-1.0 cm into the cerebellopontine angle. Division of the superior petrosal sinus may be required to gain sufficient access to the posterior fossa with larger tumors.

Generally, however, tumors that have significant volume medial to the plane of the porus acousticus are extirpated using a retrosigmoid approach if hearing is to be conserved. If hearing conservation is not an issue, the retrosigmoid approach is sometimes preferred for tumors with significant inferior extension since the lower cranial nerves are better visualized with a retrosigmoid approach. Occasionally, the retrosigmoid approach is combined with a translabyrinthine approach for such large acoustic neuromas.

## Relevant anatomy

The following anatomic variations can make the translabyrinthine approach much more difficult and at times impossible.

* High-riding jugular bulb: In some individuals, the jugular bulb may actually ride up above the level of the inferior internal auditory canal.
* Anteriorly placed sigmoid sinus: In such circumstances, the distance between the sigmoid sinus and the external auditory canal may be a few millimeters or less. Such a dramatic limitation of the space within which the surgeon has to operate not only makes a successful tumor extirpation much more difficult but puts the facial nerve and the displaced sinus itself at significantly increased risk of injury.
* Contracted sclerotic mastoid: Such mastoid cavities provide little room for tumor removal. Moreover, they are often associated with suppurative otitis media, in itself a contraindication to the translabyrinthine approach.
* Reduced or absent flow in the contralateral sinus: Previous operation, trauma, congenital anomalus development, and previous or concurrent disease can all result in markedly reduced or absent venous outflow through the contralateral sinus. In such cases, consideration may be given to a retrosigmoid approach merely because it reduces the risk of injury to the remaining sinus, occlusion of which would result in catastrophic venous infarction.

## Surgeon preference

Some surgeons have more experience and are much more comfortable with one approach relative to another. Generally, such preferences should be followed. However, if hearing conservation is a realistic option using an approach unfamiliar to the primary surgeon, consideration should be given to referring the patient to someone who is familiar with the appropriate approach.

## Patient preference

Patient preferences should be carefully considered even when they do not conform to the surgeon's judgment. Some patients are adamant about going to any lengths for hearing conservation even when the treating physician is quite convinced that the patient's hearing is so poor as to be of little or no practical utility. Some patients willingly sacrifice even good hearing if doing so even slightly enhances the possibility of successful facial nerve preservation. Some patients have very clear-cut opinions about one type of incision versus another (sometimes based on cosmetic consideration). Intraoperative Details

## Translabyrinthine approach

The translabyrinthine approach is the most versatile of the 3 common approaches to the cerebellopontine angle. The main disadvantage is profound deafness in the operated ear due to violation of the membranous labyrinth. In general, even the largest acoustic neuromas can be removed through a translabyrinthine craniotomy. In addition, the facial

nerve is found at the fundus of the internal auditory canal where the vertical crest (Bill's bar) provides a natural plane for facial nerve dissection from the superior vestibular nerve. At the author's institution, the translabyrinthine approach is preferred with any acoustic neuroma over 2 cm or in an ear with poor hearing.

The patient is laid supine and a Mayfield head frame may be used. An incision is then made two finger-breadths from the postauricular sulcus. The temporalis muscle and mastoid periosteum are identified. The skin flap is then elevated anteriorly, leaving as much periosteum down as possible. The periosteum is then incised along the linea temporalis and then towards the mastoid tip in a T-shaped fashion. This will allow a water-tight second layer for closure to prevent postoperative cerebrospinal fluid leakage. The mastoid periosteum is then elevated from the underlying mastoid bone. Often, the emissary vein is encountered and this can be controlled with bipolar coagulation and/or bone wax.

A wide cortical mastoidectomy is performed. The middle and posterior fossa dura are identified as well as the sigmoid sinus. The bone is removed from these structures to allow retraction of the temporal lobe dura and sigmoid sinus. Next, the antrum, lateral semicircular canal, and vertical facial nerve are identified.

The incus is removed and a facial recess is performed. The in tensor tympani tendon is sectioned and the eustachian tube is packed with oxidized cellulose packing. The middle ear space is then packed with temporalis muscle.

A labyrinthectomy is performed and the jugular bulb is identified. The internal auditory canal is subsequently identified and troughs are developed both superiorly and inferiorly around the internal auditory canal until approximately 270° of internal auditory canal is exposed. The remaining bone is then removed from the internal auditory canal and the facial nerve is found as it turns into the labyrinthine segment. The superior vestibular nerve is then followed out to the ampullated end of the superior semicircular canal.

At this point, the transverse crest and vertical crest (Bill's bar) are identified. The superior vestibular nerve is then reflected inferiorly from the ampullated end of the superior semicircular canal. The facial nerve can often be found superior medial to this and is confirmed using a facial nerve stimulator. At this point, the tumor is generally debulked and the facial nerve is located at the origin from the brain stem. Once the tumor is adequately debulked, the acoustic neuroma is then dissected from the facial nerve. Often, the facial nerve is very adherent to the acoustic neuroma around the porus of the internal auditory canal.

Once the tumor has been removed, the posterior fossa dura is then re-approximated. Fat is harvested from the abdomen and packed into the surgical defect. The periosteal and skin layers are closed in a water-tight fashion. The patient wears a pressure dressing for 3 days.

Retrosigmoid approach

The patient may be placed in the supine position on the operating table and with the head toward the contralateral shoulder. The true lateral or park-bench position is still used by some surgeons because it permits the occiput to be rotated a little bit more superiorly. This allows a slightly more direct view of the internal auditory canal.

The operation is performed through either a vertically oriented linear incision or an anteriorly based U-shaped flap. An occipital craniotomy is then performed. Any mastoid air cells are carefully waxed off to prevent postoperative cerebrospinal fluid leak. The dura is opened and the arachnoid incised. The cerebellum frequently falls away from the posterior surface of the temporal bone after the cisterna magna has been opened. Hyperventilation, steroids, and intraoperative diuretics (principally mannitol) are used to reduce intracranial pressure and to provide additional exposure with a limited amount of retraction. Nonetheless, gentle cerebellar retraction is occasionally required especially in larger tumors.

Once adequate exposure has been obtained, the tumor is clearly visualized along with the brain stem and lower cranial nerves. However, cranial nerves VII and VIII are rarely observed because they are almost always pushed forward and lie across the anterior surface of the tumor, which cannot be visualized. Debulking of the tumor is the next step and must be carefully performed so as to maintain the anterior portions of the capsule in order to prevent injury to cranial nerve VII and/or VIII. Once the tumor has been substantially debulked, the posterior wall of the internal auditory canal can be removed using a high-speed drill.

Great care must be taken to avoid injuring the labyrinth while removing the posterior wall of the internal auditory canal. Portions of the labyrinth quite commonly are medial to the lateral end of the internal auditory canal. Although no single anatomic landmark is completely reliable for prevention of injury to the labyrinth, the singular nerve and its canal, and the operculum of the vestibular aqueduct, are used as important surgical landmarks. Careful measurements taken from preoperative CT scans can provide useful information during drilling of the posterior wall of the internal auditory canal.

The length of the internal auditory canal varies considerably, and knowing exactly how much posterior canal wall needs to be removed to adequately expose the tumor can help limit inadvertent injury to the labyrinth. Blind extraction of tumor from the internal auditory canal without removing the posterior wall poses a significant risk to the facial and/or auditory nerve integrity and increases the chance of leaving tumor at the fundus. Use of intraoperative angled endoscopes has been reported as an adjunct in performing this phase of the operation.

Every effort should be made to prevent bone dust from entering the subarachnoid space during the intradural drilling of the internal auditory canal. One probable cause for severe and intractable postoperative headache is spillage of bone dust into the subarachnoid space during tumor removal. Surgicel, Gelfoam, Telfa pads, and/or cottonoid strips are

placed around the operative site so that bone dust adheres to them and is removed as they are removed. Once the internal auditory canal is exposed, the dura is opened and the tumor is removed. Although never proven, dissection from medial to lateral is thought to be less traumatic to both the cochlear nerve and to the vascular supply of the inner ear. The vestibular nerves are generally sacrificed, and unless hearing is to be preserved, the cochlear nerve is sacrificed as well.

Eventually, the surgeon is left with the anterior portions of the capsule adhered to the brain stem and cranial nerve VII. As the tumor capsule is carefully removed from the brain stem, the root entry zone of cranial nerve VII can be identified. The capsule is then carefully removed from the facial nerve with as little trauma as possible.

The facial nerve monitor facilitates this portion of the dissection. A meaningful amount of data now shows that results are improved when facial nerve monitoring is employed. A variety of techniques have been used to monitor the cochlear nerve when hearing preservation is desired. The most commonly used method is intraoperative ABR, but it has a number of disadvantages. Most importantly, it requires summing a large number of repetitions in order to extract a response from background noise. Consequently, a delay occurs between surgical manipulations and ABR changes. Direct cochlear nerve monitoring offers the advantage of real-time feedback, but a fully satisfactory method of placing and securing the electrode still is lacking.

Once tumor removal is complete and hemostasis is absolute, the dura is closed and the craniotomy defect is repaired, either by replacing the original bone flap or with methylmethacrylate or hydroxyapatite.

Middle cranial fossa approach

Although some surgeons use an extended middle cranial fossa approach for tumors that extend a centimeter or more outside the porus acusticus into the cerebellopontine angle, the middle cranial fossa approach is most frequently used for intracanalicular tumors. It is, by consensus, the approach of choice for small tumors that lie within the lateral portions of the internal auditory canal when hearing conservation is desired.

The head must be in the true lateral position. In young individuals with a supple neck, this can often be accomplished by turning the head to the side with the patient in the supine position. But if neck mobility is limited or concern exists that forced head turning will limit posterior fossa circulation or aggravate cervical spine disorders, then a true lateral (park-bench) position should be used.

Exposure must be centered over a vertically oriented line that passes approximately 1 cm anterior to the external auditory meatus. This is most easily accomplished through a linear incision. A posteriorly based U-shaped or curvilinear S-shaped incision can be used if concern exists about scar contracture. Depending upon the incision used, the temporalis muscle is incised or reflected inferiorly. A temporal craniotomy (approximately 5 cm by 5 cm) is performed with its base at the root of the zygoma. The

dura is elevated from the floor of the middle cranial fossa, and osmotic diuretics, head elevation, hyperventilation, and steroids are used to limit cerebral edema.

The dura of the temporal lobe is then elevated off the superior surface of the temporal bone. The anterior extent of such elevation is usually the foramen spinosum, but the middle meningeal artery can be divided between clips and elevation continued anteriorly to the foramen ovale if additional exposure is desired. Dural elevation should proceed from posterior to anterior to avoid injury to an exposed greater superficial petrosal nerve or geniculate ganglion. Bleeding from the veins associated with the middle meningeal artery is often quite brisk but can generally be controlled with oxidized cellulose packing. Medial dissection continues to the free edge of the temporal bone.

The superior petrosal sinus is attached to the posterior surface of the temporal bone but not always at its superior edge. Care must be taken to avoid injuring it. If inadvertent injury occurs, bleeding can generally be controlled with intraluminal oxidized cellulose packing, electrocautery, or hemoclips. When extended middle cranial fossa approaches are employed, the superior petrosal sinus is deliberately divided between clips.

When it can be identified easily, the arcuate eminence is an extremely helpful landmark. Careful drilling can often identify the blue line of the superior canal inferior to it. Because the most difficult exposure to achieve during middle fossa surgery is the lateral posterior end of the internal auditory canal, dissection is performed as close to the superior semicircular canal as possible. The greater superficial petrosal nerve is generally easy to visualize and can be followed retrograde to the geniculate ganglion. It lies approximately 1.0 cm directly medial to the foramen spinosum. Once the area of the geniculate is identified, small diamond burrs are used to completely expose it. If the greater superficial petrosal nerve cannot be located and no other landmarks are available, the middle ear space can be entered from above and the head of the malleus can be identified. The geniculate ganglion lies approximately 2-3 mm anterior and medial to the head of the malleus.

Once the geniculate ganglion has been completely exposed, the labyrinthine portion of the nerve can be identified and followed medially and inferiorly into the internal auditory canal. The labyrinthine portion of the nerve takes a markedly vertical and medial course as it moves from the lateral geniculate ganglion to the proximal fundus of the internal auditory canal, which lies 5 or more millimeters deep to the geniculate ganglion. Some surgeons prefer to identify the internal auditory canal medially. Once the medial end of the canal is completely identified, they follow the canal laterally to the fundus of the internal auditory canal.

The bone overlying the internal auditory canal should be removed until approximately 270 º of the internal auditory canal is exposed. The most difficult area to expose is the point at which the superior vestibular nerve penetrates the labyrinthine bone to innervate the ampulla; however, exposure in this area is critical if the anatomy of the lateral end of the internal auditory canal is to be well visualized. If the superior vestibular nerve

channel is identified, tumor removal is generally successful and relatively straightforward.

Larger tumors frequently have the facial nerve splayed out over the anterior superior portions of the tumor. Tumor removal begins, as with other approaches, by careful debulking. Once the tumor is debulked, enough room is created within the internal auditory canal to carefully remove the tumor capsule from the inferior surface of the facial nerve. Again, care must be taken to avoid torsion or twisting of the nerve during tumor removal.

Once the tumor has been completely removed, the integrity of the facial nerve is tested using the intraoperative facial nerve monitor. Presumably, the monitor has been in use throughout the case. If the facial nerve can be stimulated with low stimulus intensities, chances of good postoperative facial nerve function increase. Fat is then packed into the internal auditory canal after using bone wax to fill obvious air cells to prevent postoperative cerebrospinal fluid leak. The facial nerve monitor generally alerts the physician if fat is being packed in too tightly that the integrity of the facial nerve is being compromised. Retractors are removed, and the temporal lobe dura is allowed to relax. The bone plate is replaced using miniplates, and the wound is closed in multiple layers.

# Chapter 5

# Delayed Sleep Phase Syndrome

| Delayed sleep phase syndrome | |
|---|---|
| **ICD-10** | G47.2 |
| **ICD-9** | 327.31 |
| **eMedicine** | neuro/655 |
| **MeSH** | D021081 |

**Delayed sleep-phase syndrome** (DSPS), also known as **delayed sleep-phase disorder** (DSPD) or **delayed sleep-phase type** (DSPT), is a circadian rhythm sleep disorder, a chronic disorder of the timing of sleep, peak period of alertness, the core body temperature rhythm, hormonal and other daily rhythms, compared to the normal population and relative to societal requirements. People with DSPS generally fall asleep some hours after midnight and have difficulty waking up in the morning.

Often, people with the disorder report that they cannot sleep until early morning, but fall asleep at about the same time every "night". Unless they have another sleep disorder such as sleep apnea in addition to DSPS, patients can sleep well and have a normal need for sleep. Therefore, they find it very difficult to wake up in time for a typical school or work day. If, however, they are allowed to follow their own schedules, e.g. sleeping from 4 a.m. to noon, they sleep soundly, awaken spontaneously, and do not experience excessive daytime sleepiness.

The syndrome usually develops in early childhood or adolescence. An adolescent version disappears in adolescence or early adulthood; otherwise DSPS is a lifelong condition. Depending on the severity, it can be to a greater or lesser degree treatable. Prevalence among adults, equally distributed among women and men, is approximately 0.15%, or 3 in 2,000.

DSPS was first formally described in 1981 by Dr. Elliot D. Weitzman and others at Montefiore Medical Center. It is responsible for 7–10% of patient complaints of chronic insomnia. However, as few doctors are aware of it, it often goes untreated or is treated inappropriately; DSPS is often misdiagnosed as primary insomnia or as a psychiatric condition. At its most severe and inflexible, it is an invisible disability.

## *Definition*

According to the International Classification of Sleep Disorders (ICSD), the circadian rhythm sleep disorders share a common underlying chronophysiologic basis:

The major feature of these disorders is a misalignment between the patient's sleep pattern and the sleep pattern that is desired or regarded as the societal norm... In most circadian rhythm sleep disorders, the underlying problem is that the patient cannot sleep when sleep is desired, needed or expected.

The ICSD (page 128-133) diagnostic criteria for delayed sleep-phase syndrome are:

1. There is an intractable delay in the phase of the major sleep period in relation to the desired clock time, as evidenced by a chronic or recurrent complaint of inability to fall asleep at a desired conventional clock time together with the inability to awaken at a desired and socially acceptable time.
2. When not required to maintain a strict schedule, patients will exhibit normal sleep quality and duration for their age and maintain a delayed, but stable, phase of entrainment to local time.
3. Patients have little or no reported difficulty in maintaining sleep once sleep has begun.
4. Patients have a relatively severe to absolute inability to advance the sleep phase to earlier hours by enforcing conventional sleep and wake times.
5. Sleep-wake logs and/or actigraphy monitoring for at least two weeks document a consistent habitual pattern of sleep onsets, usually later than 2 a.m., and lengthy sleeps.
6. Occasional noncircadian days may occur (i.e., sleep is "skipped" for an entire day and night plus some portion of the following day), followed by a sleep period lasting 12 to 18 hours.
7. The symptoms do not meet the criteria for any other sleep disorder causing inability to initiate sleep or excessive sleepiness.
8. If any of the following laboratory methods is used, it must demonstrate a delay in the timing of the habitual sleep period: 1) Twenty-four-hour polysomnographic monitoring (or by means of two consecutive nights of polysomnography and an intervening multiple sleep latency test), 2) Continuous temperature monitoring showing that the time of the absolute temperature nadir is delayed into the second half of the habitual (delayed) sleep episode.

Some people with the abnormality adapt their lives to the delayed sleep phase, avoiding common business hours (e.g., 9 a.m. to 5 p.m.) as much as possible. They have the disorder, but for them it is not a disability. The ICSD's severity criteria, all of them "over at least a one-month period", are:

- Mild: Two hour delay associated with little or mild impairment of social or occupational functioning.
- Moderate: Three hour delay associated with moderate impairment.
- Severe: Four hour delay associated with severe impairment.

Some features of DSPS which distinguish it from other sleep disorders are:

- People with DSPS have at least a normal—and often much greater than normal—ability to sleep during the morning, and sometimes in the afternoon as well. In contrast, those with chronic insomnia do not find it much easier to sleep during the morning than at night.
- People with DSPS fall asleep at more or less the same time every night, and sleep comes quite rapidly if the person goes to bed near the time he or she usually falls asleep. Young children with DSPS resist going to bed before they are sleepy, but the bedtime struggles disappear if they are allowed to stay up until the time they usually fall asleep.
- DSPS patients can sleep well and regularly when they can follow their own sleep schedule, e.g. on weekends and during vacations.
- DSPS is a chronic condition. Symptoms must have been present for at least one month before a diagnosis of DSPS can be made.

Attempting to force oneself onto daytime society's schedule with DSPS has been compared to constantly living with 6 hours of jet lag; the disorder has, in fact, been referred to as "social jet lag". Often, sufferers manage only a few hours sleep a night during the working week, then compensate by sleeping until the afternoon on weekends. Sleeping in on weekends, and/or taking long naps during the day, may give people with the disorder relief from daytime sleepiness but may also perpetuate the late sleep phase.

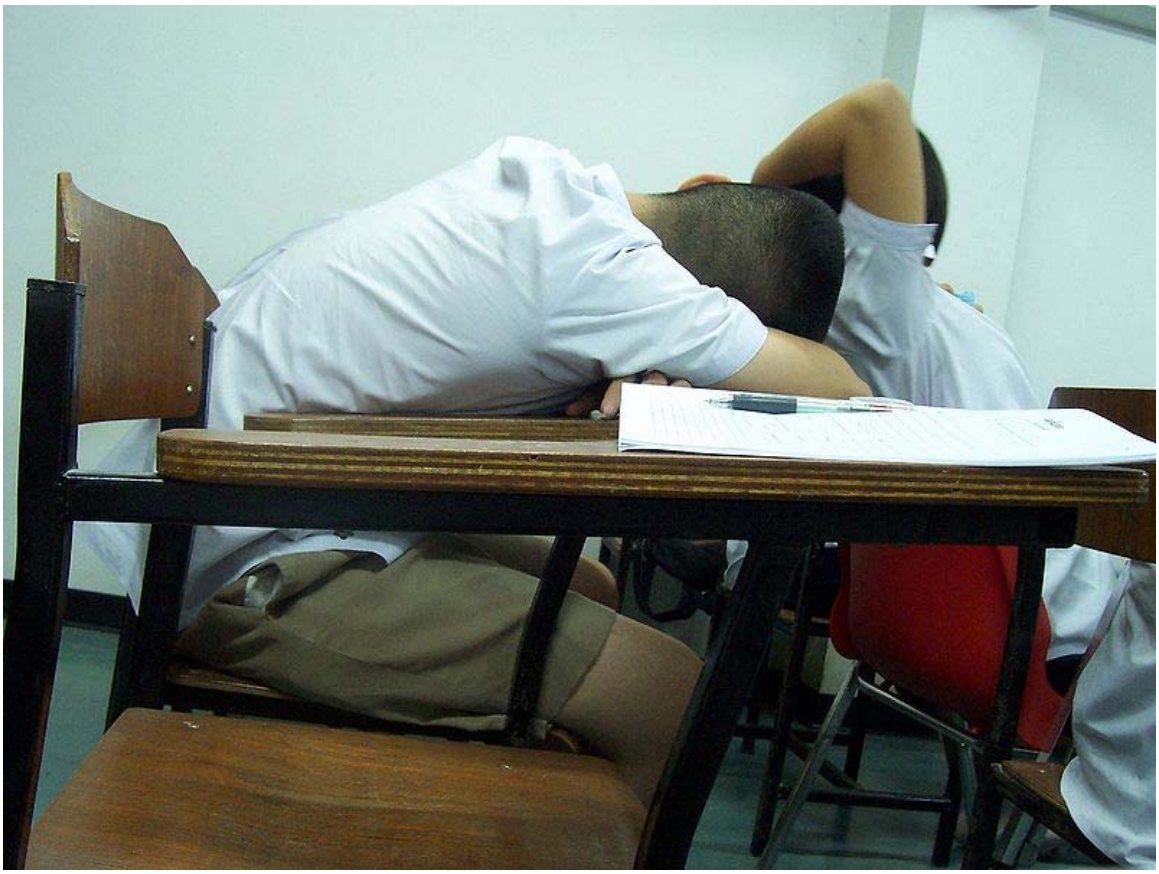
People with DSPS can be called extreme night owls. They feel most alert and say they function best and are most creative in the evening and at night. DSPS patients cannot simply force themselves to sleep early. They may toss and turn for hours in bed, and sometimes not sleep at all, before reporting to work or school. Less extreme and more flexible night owls, and indeed morning larks, are within the normal chronotype spectrum.

By the time DSPS patients seek medical help, they usually have tried many times to change their sleeping schedule. Failed tactics to sleep at earlier times may include maintaining proper sleep hygiene, relaxation techniques, early bedtimes, hypnosis, alcohol, sleeping pills, dull reading, and home remedies. DSPS patients who have tried using sedatives at night often report that the medication makes them feel tired or relaxed, but that it fails to induce sleep. They often have asked family members to help wake them in the morning, or they have used several alarm clocks. As the syndrome occurs in childhood and is most common in adolescence, it is often the patient's parents who initiate seeking help, after great difficulty waking their child in time for school.

The current formal name established in the second edition of the International Classification of Sleep Disorders is **circadian rhythm sleep disorder, delayed sleep phase type**; the preferred common name is delayed sleep-phase disorder.

## *Prevalence*

About 0.15% of adults, three in 2,000, have DSPS. Using the strict ICSD diagnostic criteria, a random study in 1993 of 7700 adults (aged 18–67) in Norway estimated the prevalence of DSPS at 0.17%. A similar study of 1525 adults (aged 15–59) in Japan estimated its prevalence at 0.13%.



Sleepy students

DSPS is not uncommon among teenagers; at least one study has indicated that the prevalence of DSPS among adolescents is as high as 7%. Among adolescents, boys predominate, while the gender distribution shows equal numbers of women and men in adults.

A marked delay of sleep patterns is a normal feature of the development of adolescent humans. According to Mary Carskadon, both circadian phase and homeostasis (the accumulation of sleep pressure during the wake period) contribute to a DSPS-like condition in post-pubertal as compared to pre-pubertal adolescents.

## *Physiology*

DSPS is a disorder of the body's timing system—the biological clock. Individuals with DSPS might have an unusually long circadian cycle, might have a reduced response to the re-setting effect of daylight on the body clock and/or may respond overly to the delaying effects of evening light and too little to the advancing effect of light earlier in the day. In support of the increased sensitivity to evening light hypothesis, "the percentage of melatonin suppression by a bright light stimulus of 1,000 lux administered 2 hours prior to the melatonin peak has been reported to be greater in 15 DSPS patients than in 15 controls."

People with normal circadian systems can generally fall asleep quickly at night if they slept too little the night before. Falling asleep earlier will in turn automatically help to advance their circadian clocks due to decreased light exposure in the evening. In contrast, people with DSPS are unable to fall asleep before their usual sleep time, even if they are sleep-deprived. Sleep deprivation does not reset the circadian clock of DSPS patients, as it does with normal people.

People with the disorder who try to live on a normal schedule cannot fall asleep at a "reasonable" hour and have extreme difficulty waking because their biological clocks are not in phase with that schedule. Normal people who do not adjust well to working a night shift have similar symptoms (diagnosed as shift-work sleep disorder, SWSD).

In most cases, it is not known what causes the abnormality in the biological clocks of DSPS patients. DSPS tends to run in families, and a growing body of evidence suggests that the problem is associated with the hPer3 (human period 3) gene. There have been several documented cases of DSPS and non-24-hour sleep-wake syndrome developing after traumatic head injury.

There have been a few cases of DSPS developing into non-24-hour sleep-wake syndrome, a more severe and debilitating disorder in which the individual sleeps later each day. It has been suggested that, instead of (or perhaps in addition to) a reduced reaction to light in the morning, an abnormal *over-sensitivity* to light in the late evening might contribute to the odd non-circadian pattern.

## *Diagnosis*


A **sleep diary** with nighttime in the middle and the weekend in the middle, the better to notice trends

DSPS is diagnosed by a clinical interview, actigraphic monitoring and/or a sleep diary kept by the patient for at least three weeks. When polysomnography is also used, it is primarily for the purpose of ruling out other disorders such as narcolepsy or sleep apnea. If a person can, on her/his own with just the help of alarm clocks and will-power, adjust to a daytime schedule, the diagnosis is not given.

DSPS is frequently misdiagnosed or dismissed. It has been named as one of the sleep disorders most commonly misdiagnosed as a primary psychiatric disorder. DSPS is often confused with: psychophysiological insomnia; depression; psychiatric disorders such as schizophrenia, ADHD or ADD; other sleep disorders; or school refusal. Practitioners of sleep medicine point out the dismally low rate of accurate diagnosis of the disorder, and have often asked for better physician education on sleep disorders.

## *Management*

Treatment, a set of management techniques, is specific to DSPS. It is different from treatment of insomnia, and recognizes the patients' ability to sleep well on their own schedules, while addressing the timing problem. Success, if any, may be partial; for example, a patient who normally awakens at noon may only attain a wake time of 10 or 10:30 with treatment and follow-up. Being consistent with the treatment is paramount.

Before starting DSPS treatment, patients are often asked to spend at least a week sleeping regularly, without napping, at the times when the patient is most comfortable. It is important for patients to start treatment well-rested.

Treatments that have been reported in the medical literature include:

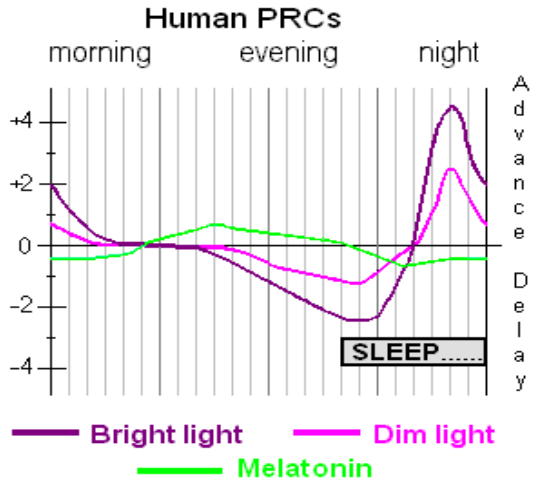
**Light therapy** (phototherapy) with a full spectrum lamp or portable visor, usually 10,000 lux for 30–90 minutes at the patient's usual time of spontaneous awakening, or shortly

before (but not long before), which is in accordance with the phase response curve (PRC) for light. The use of an LED light therapy device can reduce this to 15–30 minutes. Sunlight can also be used. Only experimentation, preferably with specialist help, will show how great an advance is possible and comfortable. For maintenance, some patients must continue the treatment indefinitely, some may reduce the daily treatment to 15 minutes, others may use the lamp, for example, just a few days a week or just every third week. Whether the treatment is successful is highly individual. Light therapy generally requires adding some extra time to the patient's morning routine. Patients with a family history of macular degeneration are advised to consult with an eye doctor. The use of exogenous melatonin administration in conjunction with light therapy is common.

**Dim lights** in the evening, sometimes called darkness therapy. Just as bright light upon awakening should advance one's sleep-phase, bright light in the evening and night delays it. One might be advised to keep lights dim the last hours before bedtime and even wear sunglasses or amber-colored goggles. Attaining an earlier sleep onset, in a dark room with eyes closed, effectively blocks a period of phase-delaying light. An understanding of this is a motivating factor in treatment.

**Chronotherapy**, which is intended to reset the circadian clock by manipulating bedtimes. Often, chronotherapy must be repeated every few months to maintain results, and its safety is uncertain. It can be one of two types. The most common consists of going to bed two or more hours *later* each day for several days until the desired bedtime is reached. A modified chronotherapy (Thorpy, 1988) is called controlled sleep deprivation with phase advance, SDPA. One stays awake one whole night and day, then goes to bed 90 minutes *earlier* than usual and maintains the new bedtime for a week. This process is repeated weekly until the desired bedtime is reached.

**Melatonin** taken an hour or so before usual bedtime may induce sleepiness.




Phase response curves for light and for melatonin administration

Taken this late, it does not, of itself, affect circadian rhythms, but a decrease in exposure to light in the evening is helpful in establishing an earlier pattern. In accordance with its phase response curve (PRC), a very small dose of melatonin can also, or instead, be taken some hours earlier as an aid to resetting the body clock; it must then be so small as to not induce excessive sleepiness.

Side effects of melatonin may include disturbance of sleep, nightmares, daytime sleepiness and depression, though the current tendency to use lower doses has decreased such complaints. Large doses of melatonin can even be counterproductive: Lewy et al. provide support to the "idea that too much melatonin may spill over onto the wrong zone of the melatonin phase-response curve." The long-term effects of melatonin administration have not been examined. In some countries the hormone is available only by prescription or not at all. In the United States and Canada, melatonin is freely available as a dietary supplement. The prescription drug Rozerem (ramelteon) is a melatonin analogue that selectively binds to the melatonin $MT_1$ and $MT_2$ receptors and, hence, has the possibility of being effective in the treatment of DSPS.

A review by a US government agency found little difference between melatonin and placebo for most primary and secondary sleep disorders. The one exception, where melatonin is effective, is the "circadian abnormality" DSPS.

**Modafinil** (Provigil) is approved in the US for treatment of shift-work sleep disorder, which shares some characteristics with DSPS, and a number of clinicians are prescribing it for DSPS patients. Modafinil does not deal with underlying causes of DSPS, but it may improve a sleep-deprived patient's quality of life. Taking modafinil less than 12 hours before the desired sleep onset time will likely exacerbate the symptoms by delaying the sleep/wake cycle.

**Trazodone** successfully treated DSPS in one elderly man.

**Vitamin $B_{12}$** was, in the 1990s, suggested as a remedy for DSPS/DSPD, and can still be found to be recommended by many sources. Several case reports were published. However, a review for the American Academy of Sleep Medicine in 2007 concluded that no benefit was seen from this treatment.

**A strict schedule** and good sleep hygiene are essential in maintaining any good effects of treatment. With treatment, some people with mild DSPS may sleep and function well with an early sleep schedule. Caffeine and other stimulant drugs to keep a person awake during the day may not be necessary, and should be avoided in the afternoon and evening, in accordance with good sleep hygiene. A chief difficulty of treating DSPS is in *maintaining* an earlier schedule after it has been established. Inevitable events of normal life, such as staying up late for a celebration or having to stay in bed with an illness, tend to reset the sleeping schedule to its intrinsic late times.

## *Prognosis*

### Adaptation to late sleeping times

Long-term success rates of treatment have seldom been evaluated. However, experienced clinicians acknowledge that DSPS is extremely difficult to treat. One study of 61 DSPS patients with mean sleep onset at about 3 a.m. and mean waking time of about 11:30 a.m., followed up with questionnaires to the subjects a year later. Good effect was seen *during* the 6-week treatment with a daily, very large dose (5 mg), of melatonin. Follow-up showed that over 90% had relapsed to pretreatment sleeping patterns within the year, 28.8% reporting that the relapse occurred within one week. The milder cases retained changes significantly longer than the more severe cases.

Working the evening or night shift, or working at home, makes DSPS less of an obstacle for some. Many of these people do not describe their pattern as a "disorder". Some DSPS individuals nap, even taking 4–5 hours of sleep in the morning and 4–5 in the evening. DSPS-friendly careers can include security work, work in theater, the entertainment industry, hospitality work in restaurants, hotels or bars, call center work, nursing, taxi or truck driving, the media, and freelance writing, translation, IT work, or medical transcription.

Some people with the disorder are unable to adapt to earlier sleeping times, even after many years of treatment. Sleep researchers have proposed that the existence of untreatable cases of DSPS be formally recognized as a "sleep-wake schedule disorder disability", an invisible disability.

Rehabilitation for DSPS patients includes acceptance of the condition, and choosing a career that allows late sleeping times, or running their own home business because it allows flexible hours. In a few schools and universities, students with DSPS have been able to arrange to take exams at times of day when their concentration levels may be good.

> “ Patients suffering from SWSD disability should be encouraged to accept the fact that they suffer from a permanent disability, and that their quality of life can only be improved if they are willing to undergo rehabilitation. It is imperative that physicians recognize the medical condition of SWSD disability in their patients and bring it to the notice of the public institutions responsible for vocational and social rehabilitation. ”

In the United States, the Americans with Disabilities Act requires that employers accommodate employees with sleeping disorders by providing appropriate accommodations. In the case of DSPS, this requires that the employer accommodate later working hours for jobs normally performed on a "9-to-5" work schedule.

## Impact on patients

Lack of public awareness of the disorder contributes to the difficulties experienced by people with DSPS, who are commonly stereotyped as undisciplined or lazy. Parents may be chastised for not giving their children acceptable sleep patterns, and schools and workplaces rarely tolerate chronically late, absent, or sleepy students and workers, failing to see them as having a chronic illness.

> “By the time DSPS sufferers receive an accurate diagnosis, they often have been misdiagnosed or labelled as lazy and incompetent workers or students for years. Misdiagnosis of circadian rhythm sleep disorders as psychiatric conditions causes considerable distress to patients and their families, and leads to some patients being inappropriately prescribed psychoactive drugs. For many patients, diagnosis of DSPS is itself a life-changing breakthrough.”

As DSPS is so little-known and so misunderstood, support groups may be important for information and self-acceptance.

People with DSPS who force themselves to live on a normal 9-5 day "are not often successful and may develop physical and psychological complaints during waking hours, i.e. sleepiness, fatigue, headache, decreased appetite, or depressed mood. Patients with [Circadian Rhythm Sleep Disorders] often have difficulty maintaining ordinary social lives, and some of them lose their jobs or fail to attend school.

## *Comorbidity*

In the DSPS cases reported in the literature, about half of the patients have suffered from clinical depression or other psychological problems, about the same proportion as among patients with chronic insomnia. According to the ICSD:

> “Although some degree of psychopathology is present in about half of adult patients with DSPS, there appears to be no particular psychiatric diagnostic category into which these patients fall. Psychopathology is not particularly more common in DSPS patients compared to patients with other forms of "insomnia." ... Whether DSPS results directly in clinical depression, or vice versa, is unknown, but many patients express considerable despair and hopelessness over sleeping normally again.”

A direct neurochemical relationship between sleep mechanisms and depression is another possibility.

It is conceivable that DSPS often has a major role in causing depression because it can be such a stressful and misunderstood disorder. A recent study from the University of

California, San Diego found no association of bipolar disorder (history of mania) with DSPD, and it states that there may be

> “ behaviorally-mediated mechanisms for comorbidity between DSPD and depression. For example, the lateness of DSPD cases and their unusual hours may lead to social opprobrium and rejection, which might be depressing... ”

The fact that half of DSPS patients are not depressed indicates that DSPS is not merely a symptom of depression. Sleep researcher M. Terman has suggested that those who follow their internal circadian clocks may be less likely to suffer from depression than those try to live on a different schedule.

DSPS patients who also suffer from depression may be best served by seeking treatment for both problems. There is some evidence that effectively treating DSPS can improve the patient's mood and make antidepressants more effective.

Vitamin D deficiency has been linked to depression. As it is a condition which comes from lack of exposure to sunlight, anyone who does not get enough sunlight exposure during the daylight hours could be at risk.

## *Accommodations*

### United States

According to the Americans with Disabilities Act of 1990, "disability" is defined as a "physical or mental impairment that substantially limits one or more major life activities". "Sleeping" is defined as a "major life activity" in § 12102(2)(a) of the statute.

# Chapter 6

# Ectrodactyly–Ectodermal Dysplasia–Cleft Syndrome

| Ectrodactyly–ectodermal dysplasia–cleft syndrome | |
|---|---|
| **OMIM** | 129900 |
| **DiseasesDB** | 34402 |

**Ectrodactyly–ectodermal dysplasia–cleft syndrome**, or **EEC**, and also referred to as **EEC syndrome** (also known as "Split hand–split foot–ectodermal dysplasia–cleft syndrome") is a rare form of ectodermal dysplasia, an autosomal dominant disorder inherited as an genetic trait. EEC is characterized by the triad of ectrodactyly, ectodermal dysplasia, and Facial Clefts. Other features noted in association with EEC include vesicoureteral reflux, recurrent urinary tract infections, obstruction of the nasolacrimal duct, decreased pigmentation of the hair and skin, missing or abnormal teeth, enamel hypoplasia, absent punctae in the lower eyelids, photophobia, occasional cognitive impairment and kidney anomalies, and conductive hearing loss.

## *Ectrodactyly*

Ectrodactyly involves the deficiency or absence of one or more central digits of the hand or foot and is also known as split hand–split foot malformation (SHFM). The hands and feet of people with ectrodactyly are often described as "claw-like" and may include only the thumb and one finger (usually either the little finger, ring finger, or a syndactyly of the two) with similar abnormalities of the feet.

Ectodermal dysplasia describes abnormalities of structures derived from the embryonic ectoderm. These abnormalities affect both the superficial ectodermal layer, as well as the mesectodermal layer constituted by the neural crest.

## *Ectodermal dysplasia*

Ectodermal dysplasia is characterized by absent sweat glands resulting in dry (hypohydrotic), often scale-like skin, sparse and usually coarse scalp hair that is often blonde, sparse eyebrows and eyelashes, and small brittle nails. In addition, abnormalities of ectodermal derivatives, neuroectodermal derivatives, and mesectodermal derivatives are often found. The ectodermal derivative abnormalities can affect the epidermis including mammary, pituitary and sweat glands, as well as hairs, dental enamel, nails, lens, and the internal ear. Neuroectodermal derivatives that can be affected include sensory placodes, cutaneous pigmental cells, and hair buds. Mesectodermal derivatives affected can include the dermis, hypodermis, dentin, head muscles and conjunctival cells, cervicofacial vascular endothelial cells, and part of the maxillofacial skeleton.

The hypohydrotic symptoms of ectodermal dysplasia described above are evidenced not only in the skin of affected individuals, but also in their phonation and voice production. Because the vocal folds may not be as hydrated as is necessary during the adduction phase of vocal fold vibration (due to lack of lubrication), a complete seal may not be accomplished between the folds and mucosal wave movement may be disrupted. This results in air escapement between the folds and the production of breathy voice, which often accompanies the skin abnormalities of ectodermal dysplasia.

## *Facial clefting*

There is much discrepancy in the literature regarding the exact nature of the facial clefting involved in EEC. Some authors claim that the clefting involved in EEC is always cleft lip +/- palate and use this marker as a means of distinguishing EEC from other syndromes, such as AEC syndrome (ankyloblepharon, ectodermal dysplasia, and clefting) in which other types of clefting are found. Other authors include cleft palate only (CPO) in conjunction with ectrodactyly and ectodermal dysplasia as sufficient for a diagnosis of EEC.

## *Speech deficits*

The speech deficits associated with EEC syndrome are numerous. The clefting often causes hypernasal speech and velopharyngeal incompetence. Because of this, compensatory articulation strategies including retruded articulation and glottal compensation are often incorporated into the patient's speech. Articulation is further impaired by the numerous dental anomalies, including missing or malformed teeth found in EEC syndrome.

Language deficits are also associated with EEC syndrome and are attributed to two factors. Conductive hearing loss due to ossicular anomalies is often encountered in patients with EEC syndrome, which can have significant impacts on language acquisition. Also, the impaired cognitive functioning that sometimes accompanies EEC can inhibit language acquisition.

## *Embryology*

The ectodermal dysplasia associated with EEC syndrome arises from abnormalities in the embryonic ectoderm, as described above. Very early in embryonic development, the embryonic stem cells differentiate into three types of cells: the ectoderm, mesoderm, and endoderm. It is from these three types of cells that all body organs originate. In general terms, ectodermal cells generate the skin, spinal cord, and teeth (as well as the numerous derivatives mentioned above). Mesodermal cells generate blood vessels, muscle and bone, and endodermal cells generate the lungs, the digestive system and the urinary system.

There are two layers of mesoderm; intraembryonic and extraembryonic. As the intraembryonic layer grows laterally, it becomes continuous with the extraembryonic layer, forming the chorion (contributing to the blood supply). At the same time during embryonic development, the ectoderm begins to thicken and fold upward, forming the neural folds, which eventually meet to form the neural tube and neural crest. Because these two events occur at roughly the same time in embryological development, abnormalities found in this syndrome can involve not only the ectodermal cells, but also disruption to development in the mesectodermal layer constituted by the neural crest.

"What these structures have in common is that their development and morphogenesis depends on the signaling between specialized ectodermal cells and the underlying mesoderm. Epithelial-mesenchymal interactions between the apical ectodermal ridge (AER) and the underlying mesenchyme, denoted the progress zone, are required for normal morphogenesis of the limb.

## *Current research*

Current research regarding EEC syndrome is focused on the genetic components contributing to the presented traits found in patients with EEC. A normal human karyotype includes 22 pairs of autosomal or non-sex chromosomes and one pair of sex chromosomes, constituting a total of 46 chromosomes. During reproduction, each parent contributes 23 chromosomes; 22 autosomal chromosomes and one sex chromosome. As stated above, EEC syndrome is an autosomal dominant disorder. This means that there is an abnormal gene on one of the autosomal (non-sex) chromosomes from either parent. Because the gene is dominant, only one parent must contribute the abnormal gene for the child to inherit the disease and the contributing parent will usually have the disease, due to the expression of the dominant gene in the parent. Some characteristics of autosomal dominant inheritance patterns include a vertical transmission pattern, meaning that the disease phenotype is seen in generation after generation. Also, the recurrence risk is 50% and there are an equal number of affected males and females. Though we can calculate the chance of inheritance of the gene, the degree of expression cannot be calculated.

## Genetics

Genetics research relating to EEC has made great strides in recent years, but many findings are currently being debated in the literature. chromosome 19, within the region of D19S894 and D19S416 has been postulated as the locus for the abnormalities found in EEC syndrome. This is supported by reports (though conflicting) regarding an association of cleft lip +/- palate on locus 19q, which suggests that EEC could be an allelic variant.

More recently, the p63 gene has been targeted in numerous studies. Interestingly, the p63 gene is a homologue of the tumor suppressor gene p53, though this is not indicative that patients with EEC are more likely to develop tumors. p63 mutations have been implicated in other human malformation conditions as well, including AEC or Hay–Wells syndrome, limb–mammary syndrome, ADULT syndrome, and non-syndromic split hand–split foot malformation. When comparing the data for these syndromes, each syndrome has a distinct pattern and type of mutations, with extensive genotype–phenotype correlations. Brunner and colleagues found that most of the p63 mutations associated with EEC "involve amino acid substitutions in the DNA binding domain common to all known p63 isoforms". The findings of their study propose that the most frequently mutated arginine codons associated with EEC are 204, 227, 279, 280, and 304, with these five amino acid mutations accounting for 75% of all reported cases of EEC syndrome. Other studies have had similar findings. One study found three of the five listed amino acid mutations in their subjects and noted that when 200 control chromosomes were tested, these three mutant alleles were not present.

## Mutations

The mutations found in EEC are missense mutations, meaning that there is a single amino acid change in the protein, as opposed to premature termination of protein synthesis, known as a nonsense mutation. The frameshift mutation introduces a premature stop codon that affected the α isotope, but does not affect the β and γ isotopes of p63. From this, it can be concluded that mutant p63α isotopes seem to play a major role in the pathogenesis of EEC syndrome. Interestingly, it seems that p63α is the predominant p63 isotope in epithelial basal cell layers, which are the cell type often associated with the anomalies found in patients with EEC syndrome.

## Genetic expression

EEC can be both familial and sporadic, both cases relating back to abnormalities of the p63 gene. This means that in some cases, EEC expresses de novo in a child of unaffected parents (sporadic) due to spontaneous mutation, in addition to the existing autosomal dominant inherited form. There seems to be significant interfamilial and intrafamilial variability in expressivity, more noticeably between rather than within families. Because of this variability, it is possible that there is more than one genetic locus involved in the actual manifestation of the syndrome in any given person. Other notably proposed sections of the involved chromosome include 3q27, and more highly disputed areas, including 7q11.2–q21.3

## Knockout mice

A study supports the hypothesis of the p63 gene as the locus for the mutations associated with EEC syndrome. The study is known as the p63 knockout mice study, in which the phenotypes of p63-deficient mice are described. The description of the mice is as follows:

P63-deficient mice lack all squamous epithelia and their derivatives, including hair, whiskers, teeth, as well as the mammary, lacrimal, and salivary glands. Particularly striking are severe limb truncations with forelimbs showing a complete absence of the phalanges and carpals, and variable defects of ulnae and radiae and hindlimbs that are lacking altogether…The p63 mutations act in a dominant fashion in humans, giving rise to a phenotype that resembles that of p63 knockout mice.

This striking data offers convincing support for the p63 gene hypothesis. This study is also cited in the demonstration that the growth and patterning of the underlying mesenchyme is highly dependent on the apical ectodermal ridge of the limbs, as well as the maxillary and mandibular branchial ectoderm that are so prominently disturbed in these mice. All of these findings are consistent with the clinical presentation of EEC in humans and may explain the association of limb malformation and clefting that are found in this syndrome.

## *Conclusion*

Further genetic research is necessary to identify and rule out other possible loci contributing to EEC syndrome, though it seems certain that disruption of the p63 gene is involved to some extent. In addition, genetic research with an emphasis on genetic syndrome differentiation should prove to be very useful in distinguishing between syndromes that present with very similar clinical findings. There is much debate in current literature regarding clinical markers for syndromic diagnoses. Genetic findings could have great implications in clinical diagnosis and treatment of not only EEC, but also many other related syndromes.

# Chapter 7

# Cardiovascular Disease

| Cardiovascular disease | |
|---|---|
| **ICD-10** | I51.6 |
| **ICD-9** | 429.2 |
| **DiseasesDB** | 28808 |
| **MeSH** | D002318 |

**Heart disease** or **cardiovascular diseases** is the class of diseases that involve the heart or blood vessels (arteries and veins). While the term technically refers to any disease that affects the cardiovascular system (as used in MeSH C14), it is usually used to refer to those related to atherosclerosis (arterial disease). These conditions usually have similar causes, mechanisms, and treatments.

In practice, cardiovascular disease is treated by cardiologists, thoracic surgeons, vascular surgeons, neurologists, and interventional radiologists, depending on the organ system that is being treated. There is considerable overlap in the specialties, and it is common for certain procedures to be performed by different types of specialists in the same hospital.

Most countries face high and increasing rates of cardiovascular disease. Each year, heart disease kills more Americans than cancer. In recent years, cardiovascular risk in women has been increasing and has killed more women than breast cancer. A large histological study (PDAY) showed vascular injury accumulates from adolescence, making primary prevention efforts necessary from childhood.

By the time that heart problems are detected, the underlying cause (atherosclerosis) is usually quite advanced, having progressed for decades. There is therefore increased emphasis on preventing atherosclerosis by modifying risk factors, such as healthy eating, exercise and avoidance of smoking.

## *Pathophysiology*

Population based studies in the youth show that the precursors of heart disease start in adolescence. The process of atherosclerosis evolves over decades, and begins as early as childhood. The Pathobiological Determinants of Atherosclerosis in Youth Study demonstrated that intimal lesions appear in all the aortas and more than half of the right coronary arteries of youths aged 7–9 years. However, most adolescents are more concerned about other risks such as HIV, accidents, and cancer than cardiovascular disease.

This is extremely important considering that 1 in 3 people will die from complications attributable to atherosclerosis. In order to stem the tide of cardiovascular disease, primary prevention is needed. Primary prevention starts with education and awareness that cardiovascular disease poses the greatest threat and measures to prevent or reverse this disease must be taken.

Obesity and diabetes mellitus are often linked to cardiovascular disease. In fact, cardiovascular disease is the most life threatening of the diabetic complications and diabetics are two- to four-fold more likely to die of cardiovascular-related causes than nondiabetics.

## *Diagnosis*

### Associated diagnostic markers

- Low-density lipoprotein
- Lipoprotein(a)
- Apolipoprotein A1
- Apolipoprotein Bho

## *Screening*

Some biomarkers are thought to offer a more detailed risk of cardiovascular disease. However, the clinical value of these biomarkers is questionable. Currently, biomarkers which may reflect a higher risk of cardiovascular disease include:

- Higher fibrinogen and PAI-1 blood concentrations
- Elevated homocysteine, or even upper half of normal
- Elevated blood levels of asymmetric dimethylarginine
- Inflammation as measured by C-reactive protein
- Elevated blood levels of brain natriuretic peptide (also known as B-type) (BNP)
- Elevated levels of NT-proBNP

## Prevention

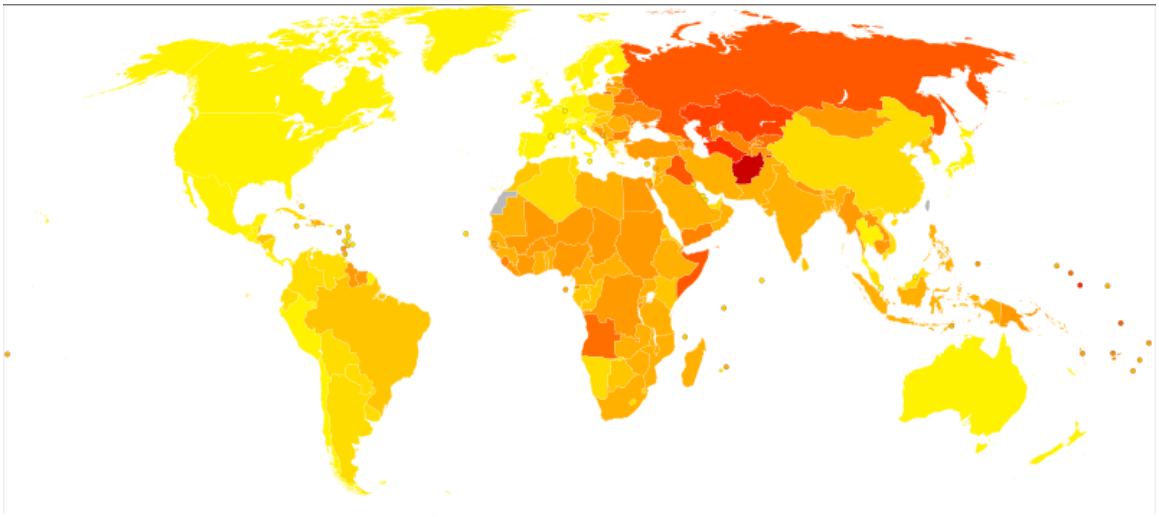
Evidence shows that the Mediterranean diet improves cardiovascular outcomes. As of 2010 however vitamins have not been found to be effective at preventing cardiovascular disease.

Modifiable risk factors to improve or prevent atherosclerosis include: diet high in fibers from vegetables while low in saturated fat and cholesterol; tobacco cessation and avoidance of second-hand smoke; decreased alcohol consumption; lower blood pressures if elevated through the use of antihypertensive medications; strict diabetes management; decrease BMI if overweight or obese; increase daily activity to 30 minutes of moderate to vigorous exercise; and decrease emotional stress in day to day life.

## Management

Cardiovascular disease is treatable with initial treatment primarily focused on diet and lifestyle interventions. Medication may also be useful for prevention.

## Epidemiology



Disability-adjusted life year for cardiovascular diseases per 100,000 inhabitants in 2004.
- no data
- less than 900
- 900-1650
- 1650-2300
- 2300-3000
- 3000-3700
- 3700-4400
- 4400-5100
- 5100-5800
- 5800-6500
- 6500-7200


## *Research*

The first studies on cardiovascular health were performed in 1949 by Jerry Morris using occupational health data and were published in 1958. The causes, prevention, and/or treatment of all forms of cardiovascular disease remain active fields of biomedical research, with hundreds of scientific studies being published on a weekly basis. A trend has emerged, particularly in the early 2000s, in which numerous studies have revealed a link between fast food and an increase in heart disease. These studies include those conducted by the Ryan Mackey Memorial Research Institute, Harvard University and the Sydney Center for Cardiovascular Health. Many major fast food chains, particularly McDonald's, have protested the methods used in these studies and have responded with healthier menu options.

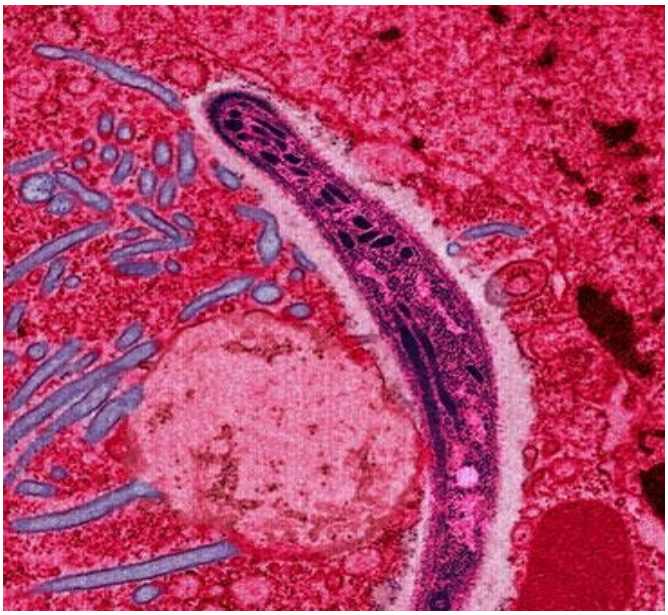
A fairly recent emphasis is on the link between low-grade inflammation that hallmarks atherosclerosis and its possible interventions. C-reactive protein (CRP) is an common inflammatory marker that has been found to be present in increased levels in patients at risk for cardiovascular disease. Also osteoprotegerin which involved with regulation of a key inflammatory transcription factor called NF-κB has been found to be a risk factor of cardiovascular disease and mortality.

Some areas currently being researched include possible links between infection with *Chlamydophila pneumoniae* and coronary artery disease. The *Chlamydia* link has become less plausible with the absence of improvement after antibiotic use.

# Chapter 8

# Infectious Disease

**Infectious disease**



A false-colored electron micrograph shows a malaria sporozoite migrating through the midgut epithelia.

| | |
|---|---|
| **ICD-10** | A00.-B99. |
| **ICD-9** | 001-139 |
| **MeSH** | D003141 |

**Infectious diseases**, also known as **communicable diseases**, or **transmissible diseases** comprise clinically evident illness (i.e., characteristic medical signs and/or symptoms of disease) resulting from the infection, presence and growth of pathogenic biological agents in an individual host organism. In certain cases, infectious diseases may be asymtomatic for much or all of their course. Infectious pathogens include some viruses, bacteria, fungi, protozoa, multicellular parasites, and aberrant proteins known as prions. These pathogens are the cause of disease epidemics, in the sense that without the pathogen, no infectious epidemic occurs.

Transmission of pathogen can occur in various ways including physical contact, contaminated food, body fluids, objects, airborne inhalation, or through vector organisms. Infectious diseases that are especially infective are sometimes called contagious and can be easily transmitted by contact with an ill person or their secretions. Infectious diseases with more specialized routes of infection, such as vector transmission, sexual transmission, are usually not regarded as contagious so do not require medical quarantine of victims.

The term *infectivity* describes the ability of an organism to enter, survive and multiply in the host, while the *infectiousness* of a disease indicates the comparative ease with which the disease is transmitted to other hosts. An infection is not synonymous with an infectious disease, as some infections do not cause illness in a host.

## Classification

Among the almost infinite varieties of microorganisms, relatively few cause disease in otherwise healthy individuals. Infectious disease results from the interplay between those few pathogens and the defenses of the hosts they infect. The appearance and severity of disease resulting from any pathogen depends upon the ability of that pathogen to damage the host as well as the ability of the host to resist the pathogen. Infectious microorganisms, or microbes, are therefore classified as either *primary pathogens* or as *opportunistic pathogens* according to the status of host defenses.

Primary pathogens cause disease as a result of their presence or activity within the normal, healthy host, and their intrinsic virulence (the severity of the disease they cause) is, in part, a necessary consequence of their need to reproduce and spread. Many of the most common primary pathogens of humans only infect humans, however many serious diseases are caused by organisms acquired from the environment or which infect non-human hosts.

Organisms which cause an infectious disease in a host with depressed resistance are classified as *opportunistic pathogens*. Opportunistic disease may be caused by microbes that are ordinarily in contact with the host, such as pathogenic bacteria or fungi in the gastrointestinal or the upper respiratory tract, and they may also result from (otherwise innocuous) microbes acquired from other hosts (as in *Clostridium difficile* colitis) or from the environment as a result of traumatic introduction (as in surgical wound infections or compound fractures). An opportunistic disease requires impairment of host defenses, which may occur as a result of genetic defects (such as Chronic granulomatous disease), exposure to antimicrobial drugs or immunosuppressive chemicals (as might occur following poisoning or cancer chemotherapy), exposure to ionizing radiation, or as a result of an infectious disease with immunosuppressive activity (such as with measles, malaria or HIV disease). Primary pathogens may also cause more severe disease in a host with depressed resistance than would normally occur in an immunosufficient host.

One way of proving that a given disease is "infectious", is to satisfy Koch's postulates (first proposed by Robert Koch), which demands that the infectious agent be identified

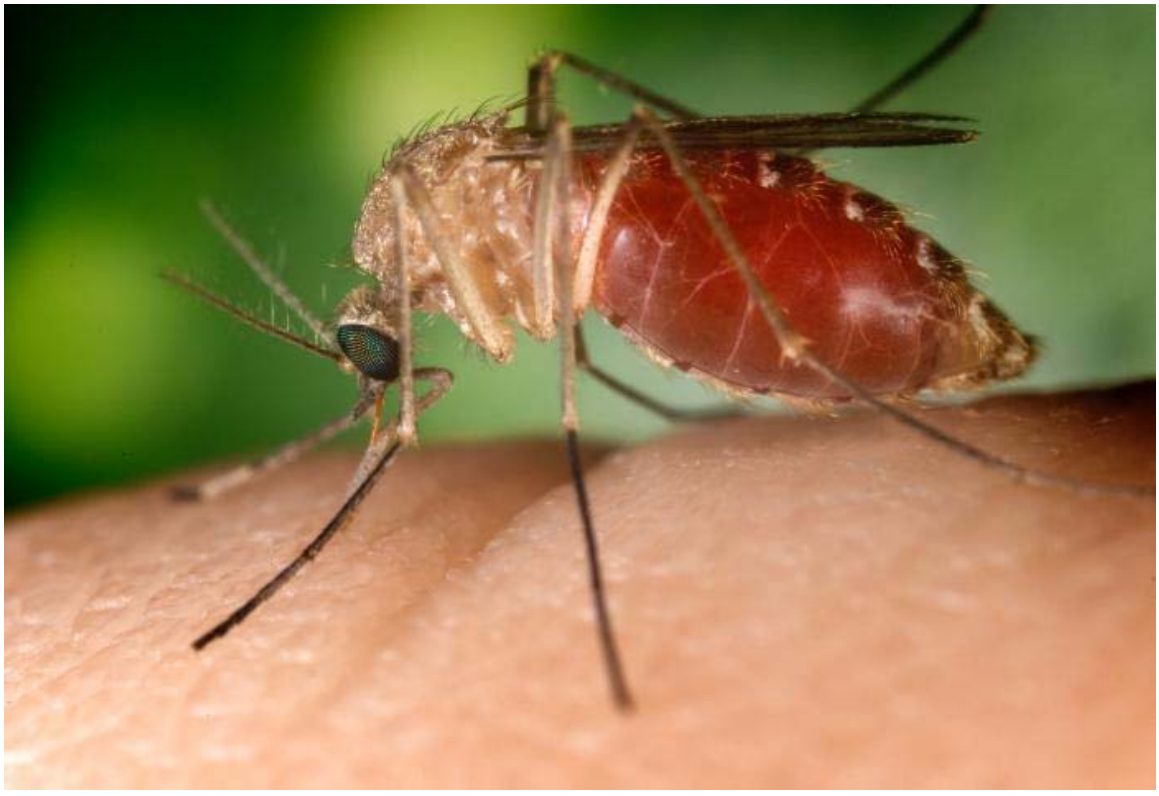
only in patients and not in healthy controls, and that patients who contract the agent also develop the disease. These postulates were first used in the discovery that Mycobacteria species cause tuberculosis. Koch's postulates can not be met ethically for many human diseases because they require experimental infection of a healthy individual with a pathogen produced as a pure culture. Often, even diseases that are quite clearly infectious do not meet the infectious criteria. For example, *Treponema pallidum*, the causative spirochete of syphilis, cannot be cultured *in vitro* - however the organism can be cultured in rabbit testes. It is less clear that a pure culture comes from an animal source serving as host than it is when derived from microbes derived from plate culture. Epidemiology is another important tool used to study disease in a population. For infectious diseases it helps to determine if a disease outbreak is sporadic (occasional occurrence), endemic (regular cases often occurring in a region), epidemic (an unusually high number of cases in a region), or pandemic (a global epidemic).

## *Transmission*

Washing one's hands, a form of hygiene, is the most effective way to prevent the spread of infectious disease.

An infectious disease is transmitted from some source. Defining the means of transmission plays an important part in understanding the biology of an infectious agent, and in addressing the disease it causes. Transmission may occur through several different mechanisms. Respiratory diseases and meningitis are commonly acquired by contact with aerosolized droplets, spread by sneezing, coughing, talking, kissing or even singing. Gastrointestinal diseases are often acquired by ingesting contaminated food and water. Sexually transmitted diseases are acquired through contact with bodily fluids, generally as a result of sexual activity. Some infectious agents may be spread as a result of contact with a contaminated, inanimate object (known as a fomite), such as a coin passed from one person to another, while other diseases penetrate the skin directly.

Transmission of infectious diseases may also involve a vector. Vectors may be mechanical or biological. A mechanical vector picks up an infectious agent on the outside of its body and transmits it in a passive manner. An example of a mechanical vector is a housefly, which lands on cow dung, contaminating its appendages with bacteria from the feces, and then lands on food prior to consumption. The pathogen never enters the body of the fly.



Culex mosquitos (*Culex quinquefasciatus* shown) are biological vectors that transmit West Nile Virus.

In contrast, biological vectors harbor pathogens within their bodies and deliver pathogens to new hosts in an active manner, usually a bite. Biological vectors are often responsible for serious blood-borne diseases, such as malaria, viral encephalitis, Chagas disease,

Lyme disease and African sleeping sickness. Biological vectors are usually, though not exclusively, arthropods, such as mosquitoes, ticks, fleas and lice. Vectors are often required in the life cycle of a pathogen. A common strategy used to control vector borne infectious diseases is to interrupt the life cycle of a pathogen by killing the vector.

The relationship between virulence and transmission is complex, and has important consequences for the long term evolution of a pathogen. Since it takes many generations for a microbe and a new host species to co-evolve, an emerging pathogen may hit its earliest victims especially hard. It is usually in the first wave of a new disease that death rates are highest. If a disease is rapidly fatal, the host may die before the microbe can get passed along to another host. However, this cost may be overwhelmed by the short term benefit of higher infectiousness if transmission is linked to virulence, as it is for instance in the case of cholera (the explosive diarrhea aids the bacterium in finding new hosts) or many respiratory infections (sneezing and coughing create infectious aerosols).

## *Prevention*

One of the ways to prevent or slow down the transmission of infectious diseases is to recognize the different characteristics of various diseases. Some critical disease characteristics that should be evaluated include virulence, distance traveled by victims, and level of contagiousness. The human strains of Ebola virus, for example, incapacitate its victims extremely quickly and kills them soon after. As a result, the victims of this disease do not have the opportunity to travel very far from the initial infection zone. Also, this virus must spread through skin lesions or permeable membranes such as the eye. Thus, the initial stage of Ebola is not very contagious since its victims experience only internal hemorrhaging. As a result of the above features, the spread of Ebola is very rapid and usually stays within a relatively confined geographical area. In contrast, the Human Immunodeficiency Virus (HIV) kills its victims very slowly by attacking their immune system. As a result, many of its victims transmit the virus to other individuals before even realizing that they are carrying the disease. Also, the relatively low virulence allows its victims to travel long distances, increasing the likelihood of an epidemic.

Another effective way to decrease the transmission rate of infectious diseases is to recognize the effects of small-world networks. In epidemics, there are often extensive interactions within hubs or groups of infected individuals and other interactions within discrete hubs of susceptible individuals. Despite the low interaction between discrete hubs, the disease can jump to and spread in a susceptible hub via a single or few interactions with an infected hub. Thus, infection rates in small-world networks can be reduced somewhat if interactions between individuals within infected hubs are eliminated (Figure 1). However, infection rates can be drastically reduced if the main focus is on the prevention of transmission jumps between hubs. The use of needle exchange programs in areas with a high density of drug users with HIV is an example of the successful implementation of this treatment method. Another example is the use of ring culling or vaccination of potentially susceptible livestock in adjacent farms to prevent the spread of the foot-and-mouth virus in 2001.

General methods to prevent transmission of pathogens may include disinfection and pest control.

## Immunity


Mary Mallon (a.k.a Typhoid Mary) was an asymptomatic carrier of typhoid fever. Over the course of her career as a cook, she infected 53 people, three of whom died.

Infection with most pathogens does not result in death of the host and the offending organism is ultimately cleared after the symptoms of the disease have waned. This process requires immune mechanisms to kill or inactivate the inoculum of the pathogen. Specific acquired immunity against infectious diseases may be mediated by antibodies and/or T lymphocytes. Immunity mediated by these two factors may be manifested by:

- a direct effect upon a pathogen, such as antibody-initiated complement-dependent bacteriolysis, opsonoization, phagocytosis and killing, as occurs for some bacteria,
- neutralization of viruses so that these organisms cannot enter cells,
- or by T lymphocytes which will kill a cell parasitized by a microorganism.

The immune system response to a microorganism often causes symptoms such as a high fever and inflammation, and has the potential to be more devastating than direct damage caused by a microbe.

Resistance to infection (immunity) may be acquired following a disease, by asymptomatic carriage of the pathogen, by harboring an organism with a similar structure (crossreacting), or by vaccination. Knowledge of the protective antigens and specific acquired host immune factors is more complete for primary pathogens than for opportunistic pathogens.

Immune resistance to an infectious disease requires a critical level of either antigen-specific antibodies and/or T cells when the host encounters the pathogen. Some individuals develop natural serum antibodies to the surface polysaccharides of some agents although they have had little or no contact with the agent, these natural antibodies confer specific protection to adults and are passively transmitted to newborns.

### Host genetic factors

The clearance of the pathogens, either treatment-induced or spontaneous, can be influenced by the genetic variants carried by the individual patients. For instance, for genotype 1 hepatitis C treated with Pegylated interferon-alpha-2a or Pegylated interferon-alpha-2b (brand names Pegasys or PEG-Intron) combined with ribavirin, it has been shown that genetic polymorphisms near the human IL28B gene, encoding interferon lambda 3, are associated with significant differences in the treatment-induced clearance of the virus. This finding, originally reported in Nature, showed that genotype 1 hepatitis C patients carrying certain genetic variant alleles near the IL28B gene are more possibly to achieve sustained virological response after the treatment than others. Later report from Nature demonstrated that the same genetic variants are also associated with the natural clearance of the genotype 1 hepatitis C virus.

## *Diagnosis*

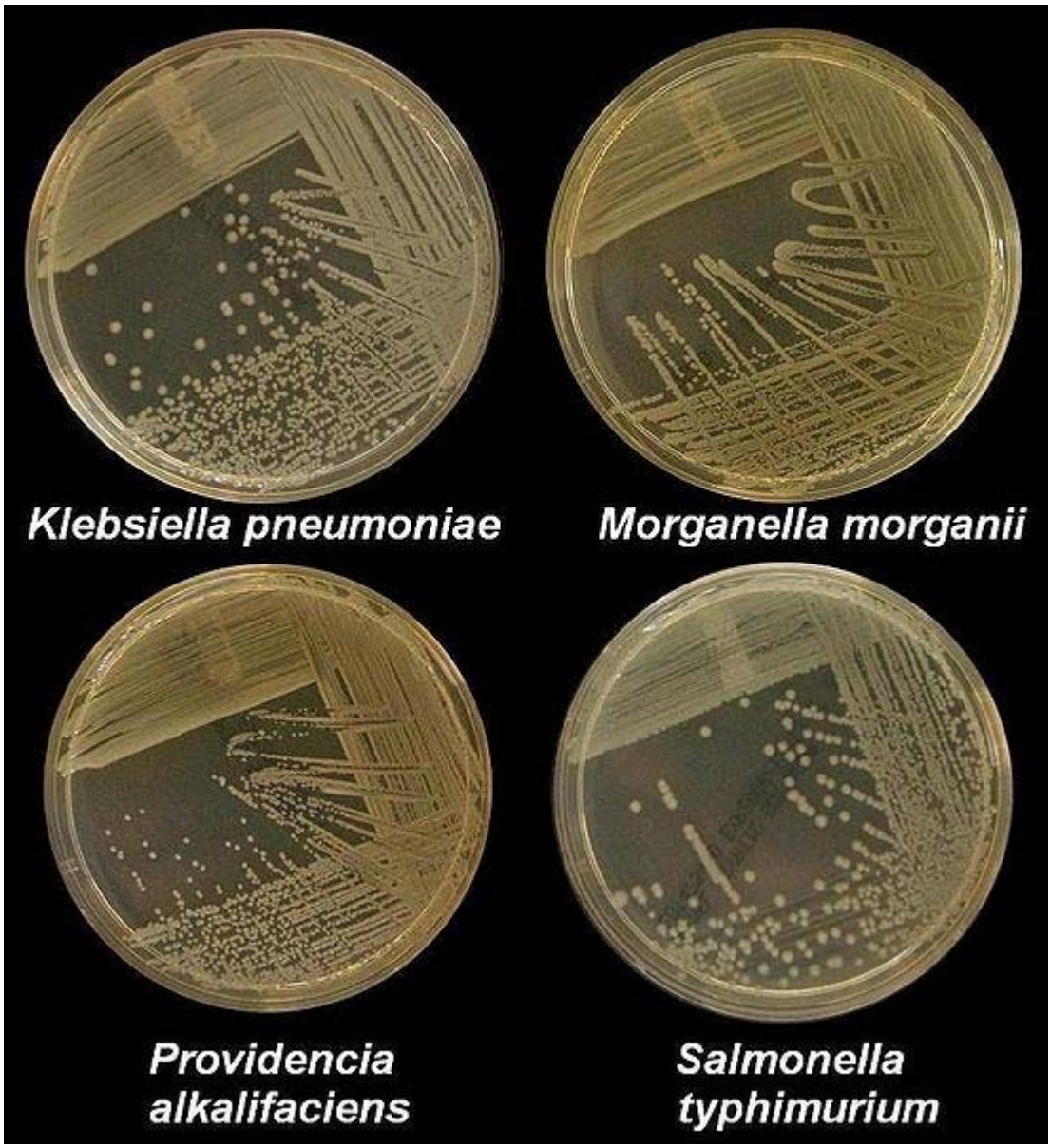
Diagnosis of infectious disease sometimes involves identifying an infectious agent either directly or indirectly. In practice most minor infectious diseases such as warts, cutaneous abscesses, respiratory system infections and diarrheal diseases are diagnosed by their clinical presentation. Conclusions about the cause of the disease are based upon the likelihood that a patient came in contact with a particular agent, the presence of a microbe in a community, and other epidemiological considerations. Given sufficient effort, all known infectious agents can be specifically identified. The benefits of identification,

however, are often greatly outweighed by the cost, as often there is no specific treatment, the cause is obvious, or the outcome of an infection is benign.

Specific identification of an infectious agent is usually only determined when such identification can aid in the treatment or prevention of the disease, or to advance knowledge of the course of an illness prior to the development of effective therapeutic or preventative measures. For example, in the early 1980s, prior to the appearance of AZT for the treatment of AIDS, the course of the disease was closely followed by monitoring the composition of patient blood samples, even though the outcome would not offer the patient any further treatment options. In part, these studies on the appearance of HIV in specific communities permitted the advancement of hypotheses as to the route of transmission of the virus. By understanding how the disease was transmitted, resources could be targeted to the communities at greatest risk in campaigns aimed at reducing the number of new infections. The specific serological diagnostic identification, and later genotypic or molecular identification, of HIV also enabled the development of hypotheses as to the temporal and geographical origins of the virus, as well as a myriad of other hypothesis. The development of molecular diagnostic tools have enabled physicians and researchers to monitor the efficacy of treatment with anti-retroviral drugs. Molecular diagnostics are now commonly used to identify HIV in healthy people long before the onset of illness and have been used to demonstrate the existence of people who are genetically resistant to HIV infection. Thus, while there still is no cure for AIDS, there is great therapeutic and predictive benefit to identifying the virus and monitoring the virus levels within the blood of infected individuals, both for the patient and for the community at large.

Diagnosis of infectious disease is nearly always initiated by medical history and physical examination. More detailed identification techniques involve the culture of infectious agents isolated from a patient. Culture allows identification of infectious organisms by examining their microscopic features, by detecting the presence of substances produced by pathogens, and by directly identifying an organism by its genotype. Other techniques (such as X-rays, CAT scans, PET scans or NMR) are used to produce images of internal abnormalities resulting from the growth of an infectious agent. The images are useful in detection of, for example, a bone abscess or a spongiform encephalopathy produced by a prion.

## Microbial culture




Four nutrient agar plates growing colonies of common Gram negative bacteria

Microbiological culture is a principal tool used to diagnose infectious disease. In a microbial culture, a growth medium is provided for a specific agent. A sample taken from potentially diseased tissue or fluid is then tested for the presence of an infectious agent able to grow within that medium. Most pathogenic bacteria are easily grown on nutrient agar, a form of solid medium that supplies carbohydrates and proteins necessary for growth of a bacterium, along with copious amounts of water. A single bacterium will grow into a visible mound on the surface of the plate called a colony, which may be separated from other colonies or melded together into a "lawn". The size, color, shape and form of a colony is characteristic of the bacterial species, its specific genetic makeup (its strain), and the environment which supports its growth. Other ingredients are often

added to the plate to aid in identification. Plates may contain substances that permit the growth of some bacteria and not others, or that change color in response to certain bacteria and not others. Bacteriological plates such as these are commonly used in the clinical identification of infectious bacterium. Microbial culture may also be used in the identification of viruses: the medium in this case being cells grown in culture that the virus can infect, and then alter or kill. In the case of viral identification, a region of dead cells results from viral growth, and is called a "plaque". Eukaryotic parasites may also be grown in culture as a means of identifying a particular agent.

In the absence of suitable plate culture techniques, some microbes require culture within live animals. Bacteria such as *Mycobacterium leprae* and *T. pallidum* can be grown in animals, although serological and microscopic techniques make the use of live animals unnecessary. Viruses are also usually identified using alternatives to growth in culture or animals. Some viruses may be grown in embryonated eggs. Another useful identification method is Xenodiagnosis, or the use of a vector to support the growth of an infectious agent. Chagas disease is the most significant example, because it is difficult to directly demonstrate the presence of the causative agent, *Trypanosoma cruzi* in a patient, which therefore makes it difficult to definitively make a diagnosis. In this case, xenodiagnosis involves the use of the vector of the Chagas agent *T. cruzi*, an uninfected triatomine bug, which takes a blood meal from a person suspected of having been infected. The bug is later inspected for growth of *T. cruzi* within its gut.

## Microscopy

Another principal tool in the diagnosis of infectious disease is microscopy. Virtually all of the culture techniques discussed above rely, at some point, on microscopic examination for definitive identification of the infectious agent. Microscopy may be carried out with simple instruments, such as the compound light microscope, or with instruments as complex as an electron microscope. Samples obtained from patients may be viewed directly under the light microscope, and can often rapidly lead to identification. Microscopy is often also used in conjunction with biochemical staining techniques, and can be made exquisitely specific when used in combination with antibody based techniques. For example, the use of antibodies made artificially fluorescent (fluorescently labeled antibodies) can be directed to bind to and identify a specific antigens present on a pathogen. A fluorescence microscope is then used to detect fluorescently labeled antibodies bound to internalized antigens within clinical samples or cultured cells. This technique is especially useful in the diagnosis of viral diseases, where the light microscope is incapable of identifying a virus directly.

Other microscopic procedures may also aid in identifying infectious agents. Almost all cells readily stain with a number of basic dyes due to the electrostatic attraction between negatively charged cellular molecules and the positive charge on the dye. A cell is normally transparent under a microscope, and using a stain increases the contrast of a cell with its background. Staining a cell with a dye such as Giemsa stain or crystal violet allows a microscopist to describe its size, shape, internal and external components and its associations with other cells. The response of bacteria to different staining procedures is

used in the taxonomic classification of microbes as well. Two methods, the Gram stain and the acid-fast stain, are the standard approaches used to classify bacteria and to diagnosis of disease. The Gram stain identifies the bacterial groups Firmicutes and Actinobacteria, both of which contain many significant human pathogens. The acid-fast staining procedure identifies the Actinobacterial genera *Mycobacterium* and *Nocardia*.

## Biochemical tests

Biochemical tests used in the identification of infectious agents include the detection of metabolic or enzymatic products characteristic of a particular infectious agent. Since bacteria ferment carbohydrates in patterns characteristic of their genus and species, the detection of fermentation products is commonly used in bacterial identification. Acids, alcohols and gases are usually detected in these tests when bacteria are grown in selective liquid or solid media.

The isolation of enzymes from infected tissue can also provide the basis of a biochemical diagnosis of an infectious disease. For example, humans can make neither RNA replicases nor reverse transcriptase, and the presence of these enzymes are characteristic of specific types of viral infections. The ability of the viral protein hemagglutinin to bind red blood cells together into a detectable matrix may also be characterized as a biochemical test for viral infection, although strictly speaking hemagglutinin is not an *enzyme* and has no metabolic function.

Serological methods are highly sensitive, specific and often extremely rapid tests used to identify microorganisms. These tests are based upon the ability of an antibody to bind specifically to an antigen. The antigen, usually a protein or carbohydrate made by an infectious agent, is bound by the antibody. This binding then sets off a chain of events that can be visibly obvious in various ways, dependent upon the test. For example, "Strep throat" is often diagnosed within minutes, and is based on the appearance of antigens made by the causative agent, *S. pyogenes*, that is retrieved from a patients throat with a cotton swab. Serological tests, if available, are usually the preferred route of identification, however the tests are costly to develop and the reagents used in the test often require refrigeration. Some serological methods are extremely costly, although when commonly used, such as with the "strep test", they can be inexpensive.

Complex serological techniques have been developed into what are known as Immunoassays. Immunoassays can use the basic antibody – antigen binding as the basis to produce an electro - magnetic or particle radiation signal, which can be detected by some form of instrumentation. Signal of unknowns can be compared to that of standards allowing quantitation of the target antigen. To aid in the diagnosis of infectious diseases, immunoassays can detect or measure antigens from either infectious agents or proteins generated by an infected organism in response to a foreign agent. For example, immunoassay A may detect the presence of a surface protein from a virus particle. Immunoassay B on the other hand may detect or measure antibodies produced by an organism's immune system which are made to neutralize and allow the destruction of the virus.

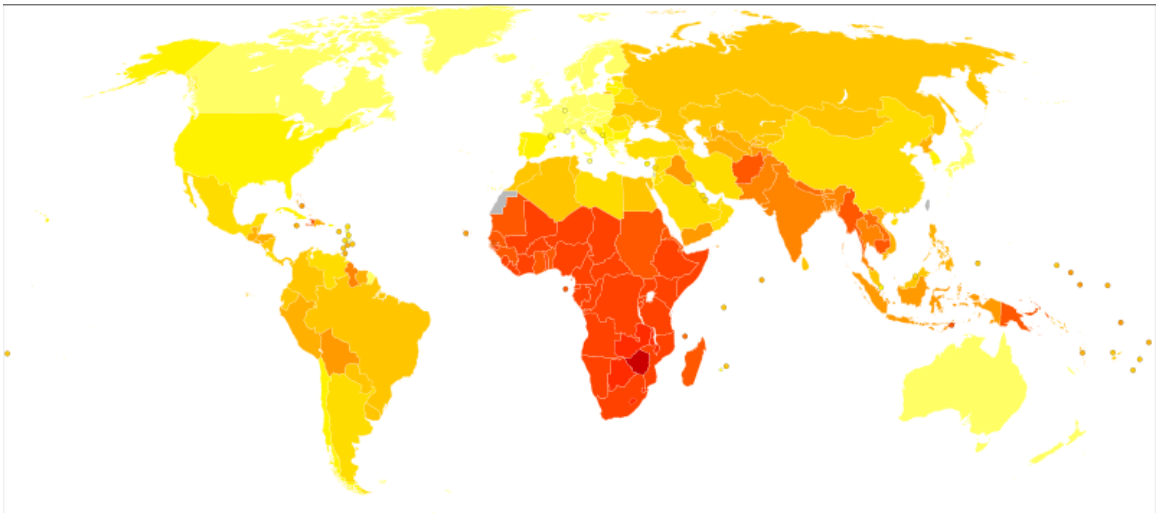
Instrumentation can be used to read extremely small signals created by secondary reactions linked to the antibody – antigen binding. Instrumentation can control sampling, reagent use, reaction times, signal detection, calculation of results, and data management to yield a cost effective automated process for diagnosis of infectious disease.

### Molecular diagnostics

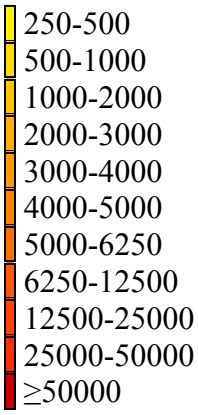
Technologies based upon the polymerase chain reaction (PCR) method will become nearly ubiquitous gold standards of diagnostics of the near future, for several reasons. First, the catalog of infectious agents has grown to the point that virtually all of the significant infectious agents of the human population have been identified. Second, an infectious agent must grow within the human body to cause disease; essentially it must amplify its own nucleic acids in order to cause a disease. This amplification of nucleic acid in infected tissue offers an opportunity to detect the infectious agent by using PCR. Third, the essential tools for directing PCR, primers, are derived from the genomes of infectious agents, and with time those genomes will be known, if they are not already.

Thus, the technological ability to detect any infectious agent rapidly and specifically are currently available. The only remaining blockades to the use of PCR as a standard tool of diagnosis are in its cost and application, neither of which is insurmountable. The diagnosis of a few diseases will not benefit from the development of PCR methods, such as some of the clostridial diseases (tetanus and botulism). These diseases are fundamentally biological poisonings by relatively small numbers of infectious bacteria that produce extremely potent neurotoxins. A significant proliferation of the infectious agent does not occur, this limits the ability of PCR to detect the presence of any bacteria.

## *Epidemiology*



Disability-adjusted life year for infectious and parasitic diseases per 100,000 inhabitants in 2004.
no data
≤250




The World Health Organization collects information on global deaths by International Classification of Disease (ICD) code categories. The following table lists the top infectious disease killers which caused more than 100,000 deaths in 2002 (estimated). 1993 data is included for comparison.

**Worldwide mortality due to infectious diseases**

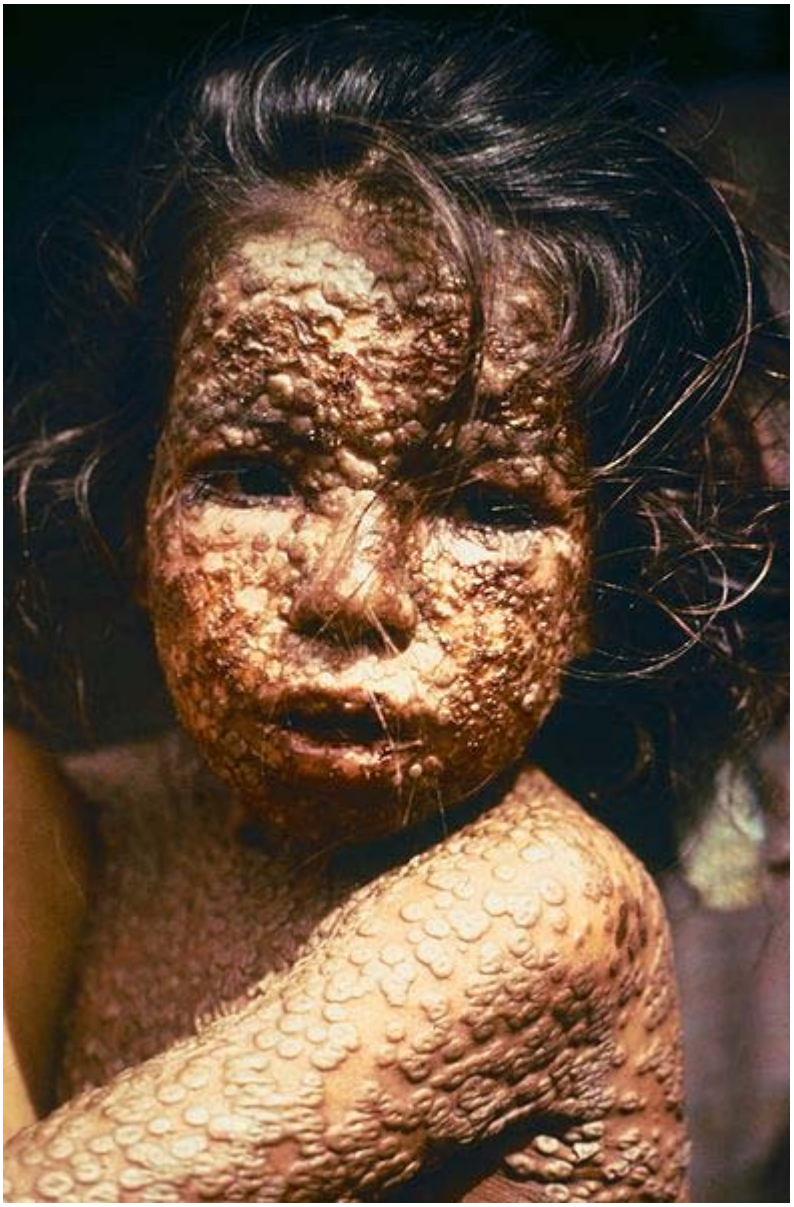
| Rank | Cause of death | Deaths 2002 (in millions) | Percentage of all deaths | Deaths 1993 (in millions) | 1993 Rank |
|---|---|---|---|---|---|
| N/A | All infectious diseases | 14.7 | 25.9% | 16.4 | 32.2% |
| 1 | Lower respiratory infections | 3.9 | 6.9% | 4.1 | 1 |
| 2 | HIV/AIDS | 2.8 | 4.9% | 0.7 | 7 |
| 3 | Diarrheal diseases | 1.8 | 3.2% | 3.0 | 2 |
| 4 | Tuberculosis (TB) | 1.6 | 2.7% | 2.7 | 3 |
| 5 | Malaria | 1.3 | 2.2% | 2.0 | 4 |
| 6 | Measles | 0.6 | 1.1% | 1.1 | 5 |
| 7 | Pertussis | 0.29 | 0.5% | 0.36 | 7 |
| 8 | Tetanus | 0.21 | 0.4% | 0.15 | 12 |
| 9 | Meningitis | 0.17 | 0.3% | 0.25 | 8 |
| 10 | Syphilis | 0.16 | 0.3% | 0.19 | 11 |
| 11 | Hepatitis B | 0.10 | 0.2% | 0.93 | 6 |
| 12-17 | Tropical diseases (6) | 0.13 | 0.2% | 0.53 | 9, 10, 16-18 |

*Note: Other causes of death include maternal and perinatal conditions (5.2%), nutritional deficiencies (0.9%),*
*noncommunicable conditions (58.8%), and injuries (9.1%).*

The top three single agent/disease killers are HIV/AIDS, TB and malaria. While the number of deaths due to nearly every disease have decreased, deaths due to HIV/AIDS have increased fourfold. Childhood diseases include pertussis, poliomyelitis, diphtheria,

measles and tetanus. Children also make up a large percentage of lower respiratory and diarrheal deaths.

## Historic pandemics



A young Bangladeshi girl infected with smallpox (1973). Due to the development of the smallpox vaccine, the disease was officially eradicated in 1979.

A pandemic (or global epidemic) is a disease that affects people over an extensive geographical area.

- Plague of Justinian, from 541 to 750, killed between 50% and 60% of Europe's population.

- The Black Death of 1347 to 1352 killed 25 million in Europe over 5 years (estimated to be between 25 and 50% of the populations of Europe, Asia, and Africa - the world population at the time was 500 million).
- The introduction of smallpox, measles, and typhus to the areas of Central and South America by European explorers during the 15th and 16th centuries caused pandemics among the native inhabitants. Between 1518 and 1568 disease pandemics are said to have caused the population of Mexico to fall from 20 million to 3 million.
- The first European influenza epidemic occurred between 1556 and 1560, with an estimated mortality rate of 20%.
- Smallpox killed an estimated 60 million Europeans during the 18th century (approximately 400,000 per year). Up to 30% of those infected, including 80% of the children under 5 years of age, died from the disease, and one third of the survivors went blind.
- In the 19th century, tuberculosis killed an estimated one-quarter of the adult population of Europe; by 1918 one in six deaths in France were still caused by TB.
- The Influenza Pandemic of 1918 (or the Spanish Flu) killed 25-50 million people (about 2% of world population of 1.7 billion). Today Influenza kills about 250,000 to 500,000 worldwide each year.

## Emerging diseases

In most cases, microorganisms live in harmony with their hosts via mutual or commensal interactions. Diseases can emerge when existing parasites become pathogenic or when new pathogenic parasites enter a new host.

1. Coevolution between parasite and host can lead to hosts becoming resistant to the parasites or the parasites may evolve greater virulence, leading to immunopathological disease.
2. Human activity is involved with many emerging infectious diseases, such as environmental change enabling a parasite to occupy new niches. When that happens, a pathogen that had been confined to a remote habitat has a wider distribution and possibly a new host organism. Parasites jumping from nonhuman to human hosts are known as zoonoses. Under disease invasion, when a parasite invades a new host species, it may become pathogenic in the new host.

Several human activities have led to the emergence and spread of new diseases:

- Encroachment on wildlife habitats. The construction of new villages and housing developments in rural areas force animals to live in dense populations, creating opportunities for microbes to mutate and emerge.
- Changes in agriculture. The introduction of new crops attracts new crop pests and the microbes they carry to farming communities, exposing people to unfamiliar diseases.

- The destruction of rain forests. As countries make use of their rain forests, by building roads through forests and clearing areas for settlement or commercial ventures, people encounter insects and other animals harboring previously unknown microorganisms.
- Uncontrolled urbanization. The rapid growth of cities in many developing countries tends to concentrate large numbers of people into crowded areas with poor sanitation. These conditions foster transmission of contagious diseases.
- Modern transport. Ships and other cargo carriers often harbor unintended "passengers", that can spread diseases to faraway destinations. While with international jet-airplane travel, people infected with a disease can carry it to distant lands, or home to their families, before their first symptoms appear.
- Pollution of the environment. Changes in the climate (such as global warming) can cause microorganisms to adapt and create new strains, which can give them an evolution advantage.

## *History*


East German postage stamps depicting four antique microscopes. Advancements in microscopy were essential to the early study of infectious diseases.

When the Black Death bubonic plague reached al-Andalus in the 14th century, Ibn Khatima and Ibn al-Khatib hypothesized that infectious diseases are caused by "contagious entities" which enter the human body. Such ideas became more popular in Europe during the Renaissance, particularly through the writing of the Italian monk Girolamo Fracastoro.

Anton van Leeuwenhoek (1632–1723) advanced the science of microscopy by being the first to observe microorganisms, allowing for easy visualization of bacteria.

In the mid-19th century John Snow and William Budd did important work demonstrating the contagiousness of typhoid and cholera through contaminated water. Both are credited with decreasing epidemics of cholera in their towns by implementing measures to prevent contamination of water.

Louis Pasteur proved beyond doubt that certain diseases are caused by infectious agents, and developed a vaccine for rabies.

Robert Koch, provided the study of infectious diseases with a scientific basis known as Koch's postulates.

Edward Jenner, Jonas Salk and Albert Sabin developed effective vaccines for smallpox and polio, which would later result in the eradication and near-eradication of these diseases, respectively.

Alexander Fleming discovered the world's first antibiotic Penicillin which Florey and Chain then developed.

Gerhard Domagk developed sulphonamides, the first broad spectrum synthetic antibacterial drugs.

## Medical specialists

The medical treatment of infectious diseases falls into the medical field of **Infectiology** and in some cases the study of propagation pertains to the field of Epidemiology. Generally, infections are initially diagnosed by primary care physicians or internal medicine specialists. For example, an "uncomplicated" pneumonia will generally be treated by the internist or the pulmonologist (lung physician).The work of the infectiologist therefore entails working with both patients and general practitioners, as well as laboratory scientists, immunologists, bacteriologists and other specialists.

An infectious disease team may be alerted when:

- The disease has not been definitively diagnosed after an initial workup
- The patient is immunocompromised (for example, in AIDS or after chemotherapy);
- The infectious agent is of an uncommon nature (e.g. tropical diseases);

- The disease has not responded to first line antibiotics;
- The disease might be dangerous to other patients, and the patient might have to be isolated

# Chapter 9

# Autoimmune Disease

| Autoimmune diseases | |
|---|---|
| **ICD-10** | D84.9, M35.9 |
| **ICD-9** | 279.4 |
| **OMIM** | 109100 |
| **DiseasesDB** | 28805 |
| **MedlinePlus** | 000816 |
| **MeSH** | D001327 |

**Autoimmune diseases** arise from an overactive immune response of the body against substances and tissues normally present in the body. In other words, the body actually attacks its own cells. The immune system mistakes some part of the body as a pathogen and attacks it. This may be restricted to certain organs (e.g. in chagas disease) or involve a particular tissue in different places (e.g. Goodpasture's disease which may affect the basement membrane in both the lung and the kidney). The treatment of autoimmune diseases is typically with immunosuppression—medication which decreases the immune response.

## *Symptoms*

The symptoms of autoimmune disease vary depending on the disease as well as the person's immune system. Common symptoms include:

- Anxiety or depression
- Blood sugar changes
- Digestive or gastrointestinal problems
- Dizziness
- Elevated fever and high body temperature
- Extreme sensitivity to cold in the hands and feet
- Fatigue
- Infertility or reduced sex drive (low libido)
- Inflammation
- Irritability

- Low or high blood pressure
- Malaise
- Weakness and stiffness in muscles and joints
- Weight Changes

And depending on the type of autoimmune disease:

- Destruction of an organ or tissue
- Increase in the size of an organ or tissue

## *Classification*

There is an on-going discussion about when a disease should be considered autoimmune, leading to different criteria such as Witebsky's postulates.

| Name: | Accepted/suspected | Hypersensitivity (I, II, III, IV, Unknown/Multiple) | Autoantibody |
|---|---|---|---|
| Achlorhydra Autoimmune Active Chronic Hepatitis | | | |
| Acute Disseminated Encephalomyelitis | | | |
| Acute hemorrhagic leukoencephalitis | | | |
| Addison's Disease | | | |
| Agammaglobulinemia | | | |
| Alopecia areata | Accepted | | T-cells |
| Amyotrophic Lateral Sclerosis | | | |
| Ankylosing Spondylitis | Accepted | | |
| Anti-GBM/TBM Nephritis | | | |
| Antiphospholipid syndrome | | | |
| Antisynthetase syndrome | | | |
| polyarticular Arthritis | Sometimes | | |
| Atopic allergy | | | |
| Atopic Dermatitis | | | |
| Autoimmune Aplastic Anemia | | | |

| | | | |
|---|---|---|---|
| Autoimmune cardiomyopathy | Accepted | | |
| Autoimmune enteropathy | | | |
| Autoimmune hemolytic anemia | Accepted | II | |
| Autoimmune hepatitis | Accepted | | |
| Autoimmune inner ear disease | Accepted | | |
| Autoimmune lymphoproliferative syndrome | Accepted | | |
| Autoimmune peripheral neuropathy | Accepted | | |
| Autoimmune pancreatitis | Accepted | | |
| Autoimmune polyendocrine syndrome Types I, II, & III | Accepted | Unknown or Multiple | |
| Autoimmune progesterone dermatitis | Accepted | | |
| Autoimmune thrombocytopenic purpura | Accepted | | |
| Autoimmune uveitis | Accepted | | |
| Balo disease/Balo concentric sclerosis | | | |
| Bechets Syndrome | | | |
| Berger's disease | | | |
| Bickerstaff's encephalitis | | | |
| Blau syndrome | | | |
| Bullous Pemphigoid | | | |
| Cancer | | | |
| Castleman's disease | | | |
| Celiac disease | Accepted | | |
| Chagas disease | Suspected | | |
| Chronic inflammatory demyelinating polyneuropathy | | | |
| Chronic recurrent multifocal osteomyelitis | | | |

| | | | |
|---|---|---|---|
| Chronic lyme disease | Suspected | | |
| Chronic obstructive pulmonary disease | Suspected | | anti-elastin, Abys against epithelial cells |
| Churg-Strauss syndrome | | | |
| Cicatricial Pemphigoid | | | |
| Coeliac Disease | Accepted | | |
| Cogan syndrome | | | |
| Cold agglutinin disease | Accepted | II | |
| Complement component 2 deficiency | | | |
| Cranial arteritis | | | |
| CREST syndrome | | | |
| Crohns Disease (one of two types of idiopathic inflammatory bowel disease "IBD") | Accepted | IV | |
| Cushing's Syndrome | | | |
| Cutaneous leukocytoclastic angiitis | | | |
| Dego's disease | | | |
| Dercum's disease | Suspected | | |
| Dermatitis herpetiformis | | | |
| Dermatomyositis | Accepted | | |
| Diabetes mellitus type 1 | Accepted | IV | Glutamic acid decarboxylase antibodies (GADA), islet cell antibodies (ICA), and insulinoma-associated autoantibodies (IA-2) |
| Diffuse cutaneous systemic sclerosis | | | |
| Dressler's syndrome | | | |
| Discoid lupus erythematosus | | | |

| | | | |
|---|---|---|---|
| Eczema | | | |
| Endometriosis | Suspected | | |
| Enthesitis-related arthritis | | | |
| Eosinophilic fasciitis | Accepted | | |
| Eosinophilic gastroenteritis | | | |
| Epidermolysis bullosa acquisita | | | |
| Erythema nodosum | | | |
| Essential mixed cryoglobulinemia | | | |
| Evan's syndrome | | | |
| Fibrodysplasia ossificans progressiva | | | |
| Fibrosing aveolitis | | | |
| Gastritis | | | |
| Gastrointestinal pemphigoid | Accepted | | |
| Giant cell arteritis | | | |
| Glomerulonephritis | Sometimes | | |
| Goodpasture's syndrome | Accepted | II | Anti-Basement Membrane Collagen Type IV Protein |
| Graves' disease | Accepted | II | |
| Guillain-Barré syndrome (GBS) | Accepted | IV | Anti-ganglioside |
| Hashimoto's encephalitis | Accepted | IV | |
| Hashimoto's thyroiditis | Accepted | IV | |
| Haemolytic anaemia | | | |
| Henoch-Schonlein purpura | | | |
| Herpes gestationis | | | |
| Hidradenitis suppurativa | Suspected | | |
| Hughes syndrome | | | |
| Hypogammaglobulinemia | | | |
| Idiopathic Inflammatory Demyelinating Diseases | | | |

| | | | |
|---|---|---|---|
| Idiopathic pulmonary fibrosis | | | |
| Idiopathic thrombocytopenic purpura | Accepted | II | |
| IgA nephropathy (Also Berger's disease) | | | |
| Inclusion body myositis | | | |
| Inflammatory demyelinating polyneuopathy | | | |
| Interstitial cystitis | Suspected | | |
| Juvenile idiopathic arthritis | | | |
| Juvenile rheumatoid arthritis | | | |
| Kawasaki's Disease | Suspected | | |
| Lambert-Eaton myasthenic syndrome | | | |
| Leukocytoclastic vasculitis | | | |
| Lichen planus | | | |
| Lichen sclerosus | | | |
| Linear IgA disease (LAD) | | | |
| Lou Gehrig's Disease (Also Amyotrophic lateral sclerosis) | | | |
| Lupoid hepatitis | | | |
| Lupus erythematosus | Accepted | III | |
| Majeed syndrome | | | |
| Ménière's disease | | | |
| Microscopic polyangiitis | | | |
| Miller-Fisher syndrome | Accepted | | |
| Mixed Connective Tissue Disease | Accepted | | |
| Morphea | Suspected | | |
| Mucha-Habermann disease | | | |

| | | | |
|---|---|---|---|
| Muckle–Wells syndrome | | | |
| Multiple Myeloma | | | |
| Multiple Sclerosis | Suspected | | |
| Myasthenia gravis | Accepted | II | |
| Myositis | | | |
| Narcolepsy | Accepted | | |
| Neuromyelitis optica (Also Devic's Disease) | | | |
| Neuromyotonia | Suspected | | |
| Occular cicatricial pemphigoid | | | |
| Opsoclonus myoclonus syndrome | Suspected | | |
| Ord thyroiditis | | | |
| Palindromic rheumatism | | | |
| PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus) | | | |
| Paraneoplastic cerebellar degeneration | | | |
| Paroxysmal nocturnal hemoglobinuria (PNH) | Sometimes(?) | | |
| Parry Romberg syndrome | | | |
| Parsonnage-Turner syndrome | | | |
| Pars planitis | | | |
| Pemphigus | | | |
| Pemphigus vulgaris | Accepted | II | Anti-Desmogein 3 |
| Pernicious anaemia | Accepted | II | |
| Perivenous encephalomyelitis | | | |
| POEMS syndrome | | | |
| Polyarteritis nodosa | | | |
| Polymyalgia rheumatica | | | |
| Polymyositis | Accepted | | |

| | | | |
|---|---|---|---|
| Primary biliary cirrhosis | Accepted | | Anti-p62, Anti-sp100, Anti-Mitochondrial(M2) |
| Primary sclerosing cholangitis | | | |
| Progressive inflammatory neuropathy | Suspected | | |
| Psoriasis | Accepted | | T-cells |
| Psoriatic Arthritis | Accepted | | |
| Pyoderma gangrenosum | | | |
| Pure red cell aplasia | | | |
| Rasmussen's encephalitis | | | |
| Raynaud phenomenon | | | Suspected |
| Relapsing polychondritis | Accepted | | |
| Reiter's syndrome | | | |
| Restless leg syndrome | Suspected | | |
| Retroperitoneal fibrosis | | | |
| Rheumatoid arthritis | Accepted | III | Rheumatoid factor, Anti-MCV |
| Rheumatoid fever | | | |
| Sarcoidosis | Suspected | | |
| Schizophrenia | Suspected | | |
| Schmidt syndrome | | | |
| Schnitzler syndrome | | | |
| Scleritis | | | |
| Scleroderma | Suspected | | Anti-topoisomerase |
| Sjögren's syndrome | Accepted | | |
| Spondyloarthropathy | | | |
| Sticky blood syndrome | | | |
| Still's Disease | | | |
| Stiff person syndrome | Suspected | | |
| Subacute bacterial endocarditis (SBE) | | | |
| Susac's syndrome | | | |
| Sweet syndrome | | | |

| | | | |
|---|---|---|---|
| Sydenham Chorea | | | |
| Sympathetic ophthalmia | | | |
| Takayasu's arteritis | | | |
| Temporal arteritis (also known as "giant cell arteritis") | Accepted | IV | |
| Tolosa-Hunt syndrome | | | |
| Transverse Myelitis | | | |
| Ulcerative Colitis (one of two types of idiopathic inflammatory bowel disease "IBD") | Accepted | IV | |
| Undifferentiated connective tissue disease | Accepted | | |
| Undifferentiated spondyloarthropathy | | | |
| Vasculitis | Accepted | III | |
| Vitiligo | Suspected | | |
| Wegener's granulomatosis | Accepted | | Anti-neutrophil cytoplasmic(cANCA) |
| Wilson's syndrome | | | |
| Wiskott-Aldrich syndrome | | | |

## *Development of therapies*

In both autoimmune and inflammatory diseases the condition arises through aberrant reactions of the human adaptive or innate immune systems. In autoimmunity, the patient’s immune system is activated against the body's own proteins. In inflammatory diseases, it is the overreaction of the immune system, and its subsequent downstream signaling (TNF, IFN, etc.), which causes problems.

A substantial minority of the population suffers from these diseases, which are often chronic, debilitating, and life-threatening. There are more than eighty illnesses caused by autoimmunity. It has been estimated that autoimmune diseases are among the ten leading causes of death among women in all age groups up to 65 years.

Currently, a considerable amount of research is being conducted into treatment of these conditions. According to a report from Frost & Sullivan, the total payouts by an alliance of leading pharmaceutical companies for drug discovery contract research in the autoimmune/inflammation segment from 1997 to 2002 totaled $489.8 million, where Eli

Lilly, Suntory, Procter & Gamble, Encysive, and Novartis together account for 98.6 percent of payouts by that alliance.

# Chapter 10

# Acute Disseminated Encephalomyelitis

| Acute disseminated encephalomyelitis | |
|---|---|
| **ICD-10** | G04.0 |
| **ICD-9** | 323.61 |
| **DiseasesDB** | 158 |
| **eMedicine** | neuro/500 |
| **MeSH** | D004673 |

**Acute disseminated encephalomyelitis** (**ADEM**) is an immune mediated disease of the brain. It usually occurs following a viral infection but may appear following vaccination, bacterial or parasitic infection, or even appear spontaneously. As it involves autoimmune demyelination, it is similar to multiple sclerosis, and is considered part of the Multiple sclerosis borderline diseases. The incidence rate is about 8 per 1,000,000 people per year. Although it occurs in all ages, most reported cases are in children and adolescents, with the average age around 5 to 8 years old. The mortality rate may be as high as 5%, full recovery is seen in 50 to 75% of cases, while up to 70 to 90% recover with some minor residual disability. The average time to recover is one to six months.

ADEM produces multiple inflammatory lesions in the brain and spinal cord, particularly in the white matter. Usually these are found in the subcortical and central white matter and cortical gray-white junction of both cerebral hemispheres, cerebellum, brainstem, and spinal cord, but periventricular white matter and gray matter of the cortex, thalami and basal ganglia may also be involved.

When the patient suffers more than one demyelinating episode, it is called **Recurrent disseminated encephalomyelitis** or **Multiphasic disseminated encephalomyelitis**(MDEM).

## *Causes and antecedent history*

Viral infections thought to induce ADEM include influenza virus, enterovirus, measles, mumps, rubella, varicella zoster, Epstein Barr virus, cytomegalovirus, herpes simplex

virus, hepatitis A, and coxsackievirus; while the bacterial infections include Mycoplasma pneumoniae, Borrelia burgdorferi, Leptospira, and beta-hemolytic Streptococci. The only vaccine proven to induce ADEM is the Semple form of the rabies vaccine, but hepatitis B, pertussis, diphtheria, measles, mumps, rubella, pneumococcus, varicella, influenza, Japanese encephalitis, and polio vaccines have all been implicated. In rare cases, ADEM seems to follow from organ transplantation. The risk of ADEM from measles vaccination is about 1 to 2 per million, which is far lower than the risk of developing ADEM from an actual measles infection, which is about 1 per 1000 for measles (and 1 per 5000 for rubella). Measles infection also appears to lead to worse ADEM outcomes than cases associated with measles immunization. Some vaccines, later shown to have been contaminated with host animal CNS tissue, have ADEM incident rates as high as 1 in 600.

## *Presentation*

ADEM has an abrupt onset and a monophasic course. Symptoms usually begin 1–3 weeks after infection or vaccination. Major symptoms include fever, headache, drowsiness, seizures and coma. Although initially the symptoms are usually mild, they worsen rapidly over the course of hours to days, with the average time to maximum severity being about four and a half days. Additional symptoms include hemiparesis, paraparesis, and cranial nerve palsies.

## *Treatment*

No controlled clinical trials have been conducted on ADEM treatment, but aggressive treatment aimed at rapidly reducing inflammation of the CNS is standard. The widely accepted first-line treatment is high doses of intravenous corticosteroids, such as methylprednisolone or dexamethasone, followed by 3–6 weeks of gradually lower oral doses of prednisolone. Patients treated with methylprednisolone have shown better outcomes than those treated with dexamethasone. Oral tapers of less than three weeks duration show a higher chance of relapsing, and tend to show poorer outcomes. Other antiinflamatory and immunosuppressive therapies have been reported to show beneficial effect, such as plasmapheresis, high doses of intravenous immunoglobulin (IVIg), mitoxantrone and cyclophosphamide. These are considered alternative therapies, used when corticosteroids cannot be used, or fail to show an effect.

There is some evidence to suggest that patients may respond to a combination of methylprednisolone and immunoglobulins if they fail to respond to either separately In a study of 16 children with ADEM, 10 recovered completely after high-dose methylprednisolone, one severe case that failed to respond to steroids recovered completely after IVIg; the five most severe cases -with ADAM and severe peripheral neuropathy- were treated with combined high-dose methylprednisolone and immunoglobulin, two remained paraplegic, one had motor and cognitive handicaps, and two recovered. A recent review of IVIg treatment of ADEM (of which the previous study formed the bulk of the cases) found that 70% of children showed complete recovery after treatment with IVIg, or IVIg plus corticosteroids. A study of IVIg treatment in adults

with ADEM showed that IVIg seems more effective in treating sensory and motor disturbances, while steroids seem more effective in treating impairments of cognition, consciousness and rigor. This same study found one subject, a 71 year old man who had not responded to steroids, that responded to a IVIg treatment 58 days after disease onset.

## *Prognosis*

Full recovery is seen in 50 to 70% of cases, ranging to 70 to 90% recovery with some minor residual disability (typically assessed using measures such as mRS or EDSS), average time to recover is one to six months. The mortality rate may be as high as 5%. Poorer outcomes are associated with unresponsiveness to steroid therapy, unusually severe neurological symptoms, or sudden onset. Children tend to have more favorable outcomes than adults, and cases presenting without fevers tend to have poorer outcomes. The latter effect may be due to either protective effects of fever, or that diagnosis and treatment is sought more rapidly when fever is present.

### Motor deficits

Residual motor deficits are estimated to remain in about 8 to 30% of cases, the range in severity from mild clumsiness to ataxia and hemiparesis.

### Neurocognitive

Patients with demyelinating illnesses, such as MS, have shown cognitive deficits even when there is minimal physical disability. Research suggests that similar effects are seen after ADEM, but that the deficits are less severe than those seen in MS. A study of six children with ADEM (mean age at presentation 7.7 years) were tested for a range of neurocognitive tests after an average of 3.5 years of recovery. All six children performed in the normal range on most tests, including verbal IQ and performance IQ, but performed at least one standard deviation below age norms in at least one cognitive domain, such as complex attention (one child), short-term memory (one child) and internalizing behaviour/affect (two children). Group means for each cognitive domain were all within one standard deviation of age norms, demonstrating that, as a group, they were normal. These deficits were less severe than those seen in similar aged children with a diagnosis of MS.

Another study compared nineteen children with a history of ADEM, of which 10 were five years of age or younger at the time (average age 3.8 years old, tested an average of 3.9 years later) and nine were older (mean age 7.7y at time of ADEM, tested an average of 2.2 years later) to nineteen matched controls. Scores on IQ tests and educational achievement were lower for the young onset ADEM group (average IQ 90) compared to the late onset (average IQ 100) and control groups (average IQ 106), while the late onset ADEM children scored lower on verbal processing speed. Again, all groups means were within one standard deviation of the controls, meaning that while effects were statistically reliable, the children were as a whole, still within the normal range. There were also more

behavioural problems in the early onset group, although there is some suggestion that this may be due, at least in part, to the stress of hospitalization at a young age.

## *ADEM and multiple sclerosis*

While ADEM and MS both involve autoimmune demyelination, they differ in many clinical, genetic, imaging, and histopathological aspects. Some authors consider MS and its borderline forms to constitute a spectrum, differing only in chronicity, severity, and clinical course, while others consider them discretely different diseases.

Problems for differential diagnosis increase due to the lack of agreement for a definition of Multiple Sclerosis. For some people MS should be considered a clinical entity based in inflammatory lesions separated in time and space. As some cases of ADEM satisfy these conditions, they should be considered inside the MS spectrum. Using a pathological definition instead, they would be appart (plaques in the white matter in MS are sharply delineated, while the inflammation in ADEM is widely disseminated and ill-defined).

## *Acute hemorrhagic leukoencephalitis*

Acute hemorrhagic leukoencephalitis (AHL, or AHLE), also known as acute necrotizing encephalopathy (ANE), acute hemorrhagic encephalomyelitis (AHEM), acute necrotizing hemorrhagic leukoencephalitis (ANHLE), Weston-Hurst syndrome, or Hurst's disease, is a hyperacute and frequently fatal form of ADEM. AHL is relatively rare (less than 100 cases have been reported in the medical literature as of 2006), it is seen in about 2% of ADEM cases, and is characterized by necrotizing vasculitis of venules and hemorrhage, and edema. Death is common in the first week and overall mortality is about 70%, but increasing evidence points to favorable outcomes after aggressive treatment with corticosteroids, immunoglobulins, cyclophosphamide, and plasma exchange. About 70% of survivors show residual neurological deficits, but some survivors have shown surprisingly little deficit considering the magnitude of the white matter affected. This disease has been occasionally associated with ulcerative colitis and Crohn's disease, septicemia associated with immune complex deposition, methanol poisoning and other underlying conditions.

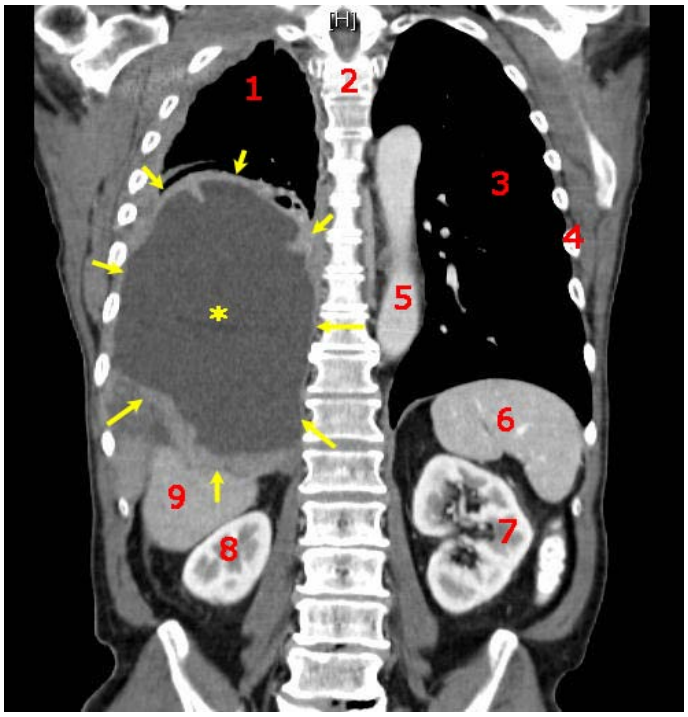
## *Experimental allergic encephalomyelitis*

Experimental allergic encephalomyelitis (EAE) is an animal model of CNS inflammation and demyelination frequently used to investigate potential MS treatments. An acute monophasic illness, EAE is far more similar to ADEM than MS.

# Chapter 11

# Cancer

**Cancer**




A coronal CT scan showing a cancer of right pleural membranes, the outer surface of the lung and inner surface of the chest wall, **malignant mesothelioma**.
Legend: → tumor ←, ★ central pleural effusion, 1 & 3 lungs, 2 spine, 4 ribs, 5 aorta, 6 spleen, 7 & 8 kidneys, 9 liver.

| | |
|---|---|
| **ICD-10** | D00. |
| **ICD-9** | 140—239 |
| **DiseasesDB** | 28843 |

| | |
|---|---|
| **MedlinePlus** | 001289 |
| **MeSH** | D009369 |

**Cancer** (medical term: malignant neoplasm) is a class of diseases in which a group of cells display uncontrolled growth, invasion that intrudes upon and destroys adjacent tissues, and sometimes metastasis, or spreading to other locations in the body via lymph or blood. These three malignant properties of cancers differentiate them from benign tumors, which do not invade or metastasize.

Researchers divide the causes of cancer into two groups: those with a hereditary genetic cause and those an environmental cause. *Environmental* in this sense means all non-hereditary factors, and encompasses far more than environmental pollution. About 5-10% of cancers are directly due to hereditary genetic factors. The remaining 90-95% of cases are due to environmental factors, such as old age, lifestyle choices, tobacco use, dietary choices, obesity, infections, radiation, lack of physical activity, and environmental pollutants. These environmental factors cause or enhance non-hereditary abnormalities in the genetic material of cells. Cell reproduction is an extremely complex process that is normally tightly regulated by several classes of genes, including oncogenes and tumor suppressor genes. Hereditary or acquired abnormalities in these regulatory genes can lead to the development of cancer.

The presence of cancer can be suspected on the basis of symptoms, or findings on radiology. Definitive diagnosis of cancer, however, requires the microscopic examination of a biopsy specimen. Most cancers can be treated. Possible treatments include chemotherapy, radiotherapy and surgery. The prognosis is influenced by the type of cancer and the extent of disease. While cancer can affect people of all ages, and a few types of cancer are more common in children, the overall risk of developing cancer increases with age. In 2007 cancer caused about 13% of all human deaths worldwide (7.9 million), and the number of cases is rising as more people live to old age.

## *Classification*

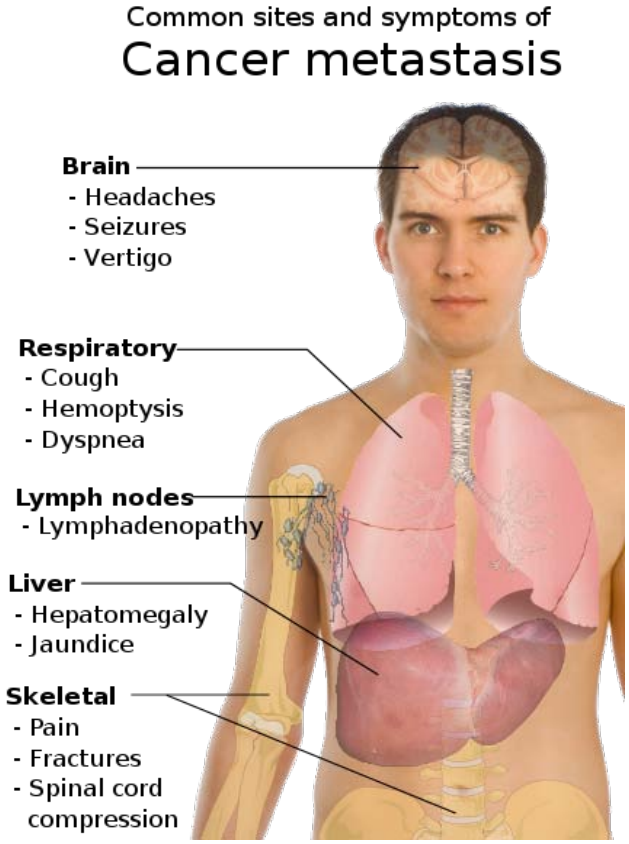
Cancers are classified by the type of cell that the tumor resembles and is therefore presumed to be the origin of the tumor. These types include:

- Carcinoma: Cancer derived from epithelial cells. This group includes many of the most common cancers, including those of the breast, prostate, lung and colon.
- Sarcoma: Cancer derived from connective tissue, or mesenchymal cells.
- Lymphoma and leukemia: Cancer derived from hematopoietic (blood-forming) cells
- Germ cell tumor: Cancer derived from pluripotent cells. In adults these are most often found in the testicle and ovary, but are more common in babies and young children.
- Blastoma: Cancer derived from immature "precursor" or embryonic tissue. These are also commonest in children.

Cancers are usually named using -carcinoma, -sarcoma or -blastoma as a suffix, with the Latin or Greek word for the organ or tissue of origin as the root. For example, a cancer of the liver is called *hepatocarcinoma*; a cancer of fat cells is called a *liposarcoma*. For some common cancers, the English organ name is used. For example, the most common type of breast cancer is called *ductal carcinoma of the breast*. Here, the adjective *ductal* refers to the appearance of the cancer under the microscope, which suggests that it has originated in the milk ducts.

Benign tumors (which are not cancers) are named using -oma as a suffix with the organ name as the root. For example, a benign tumor of smooth muscle cells is called a *leiomyoma* (the common name of this frequently occurring benign tumor in the uterus is *fibroid*). Confusingly, some types of cancer also use the -oma suffix, examples including melanoma and seminoma.

## *Signs and symptoms*




Symptoms of cancer metastasis depend on the location of the tumor

Cancer symptoms can be divided into three groups:

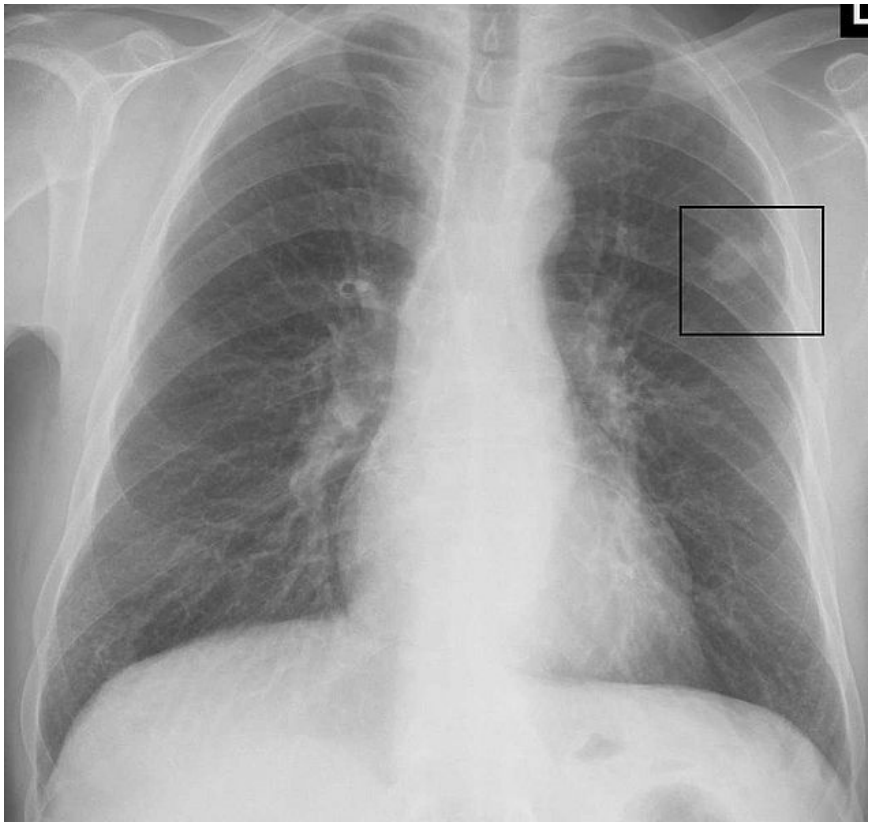
- *Local symptoms*: are restricted to the site of the primary cancer. They can include lumps or swelling (tumor), hemorrhage (bleeding from the skin, mouth or anus),

ulceration and pain. Although local pain commonly occurs in advanced cancer, the initial swelling is often painless.

- *Metastatic symptoms*: are due to the spread of cancer to other locations in the body. They can include enlarged lymph nodes (which can be felt or sometimes seen under the skin), hepatomegaly (enlarged liver) or splenomegaly (enlarged spleen) which can be felt in the abdomen, pain or fracture of affected bones, and neurological symptoms.
- *Systemic symptoms*: occur due to distant effects of the cancer that are not related to direct or metastatic spread. Some of these effects can include weight loss (poor appetite and cachexia), fatigue, excessive sweating (especially night sweats), anemia (low blood count) and other specific conditions termed paraneoplastic phenomena. These may be mediated by immunological or hormonal signals from the cancer cells.

None of these are diagnostic, as many of these symptoms commonly occur in patients who do *not* have cancer.

## *Diagnosis*



Chest x-ray showing lung cancer in the left lung

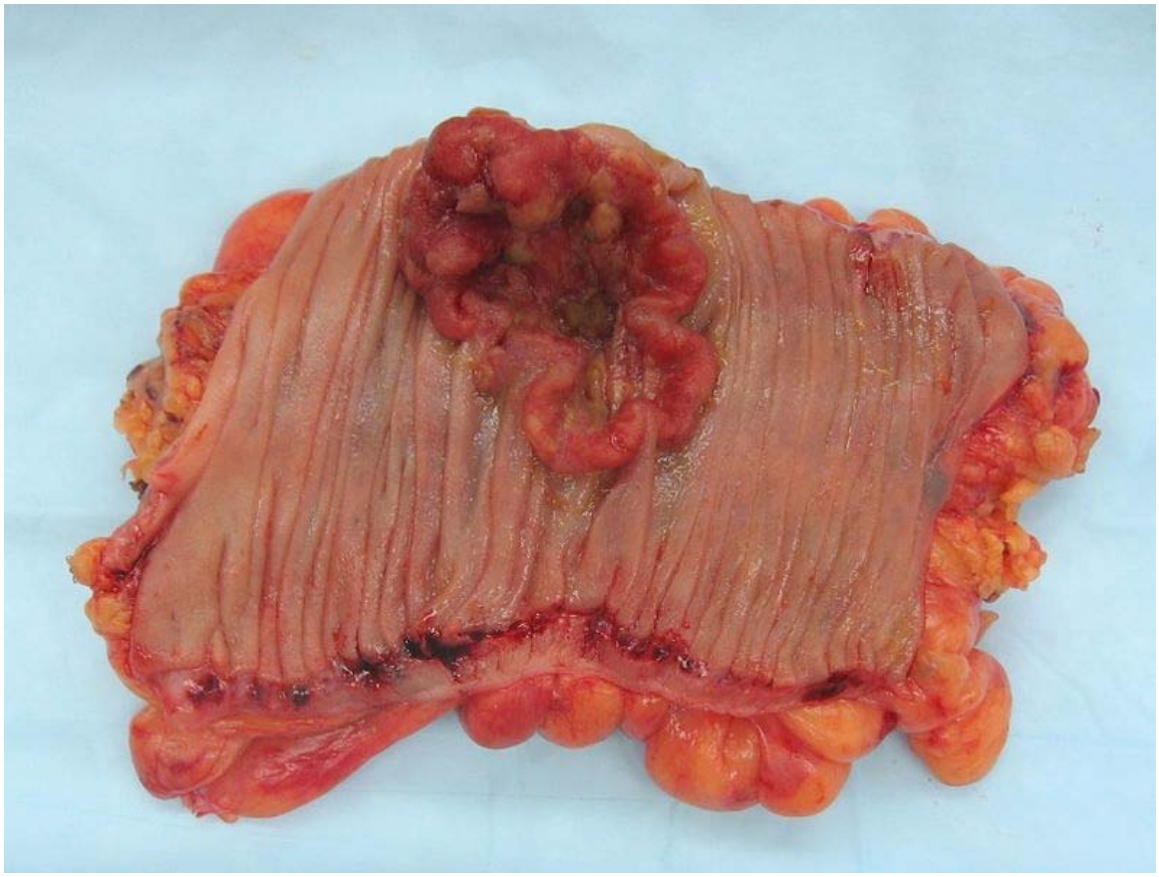
Most cancers are initially recognized either because signs or symptoms appear or through screening. Neither of these lead to a definitive diagnosis, which usually requires the opinion of a pathologist, a type of physician (medical doctor) who specializes in the

diagnosis of cancer and other diseases. People with suspected cancer are investigated with medical tests. These commonly include blood tests, X-rays, CT scans and endoscopy.

## Pathology

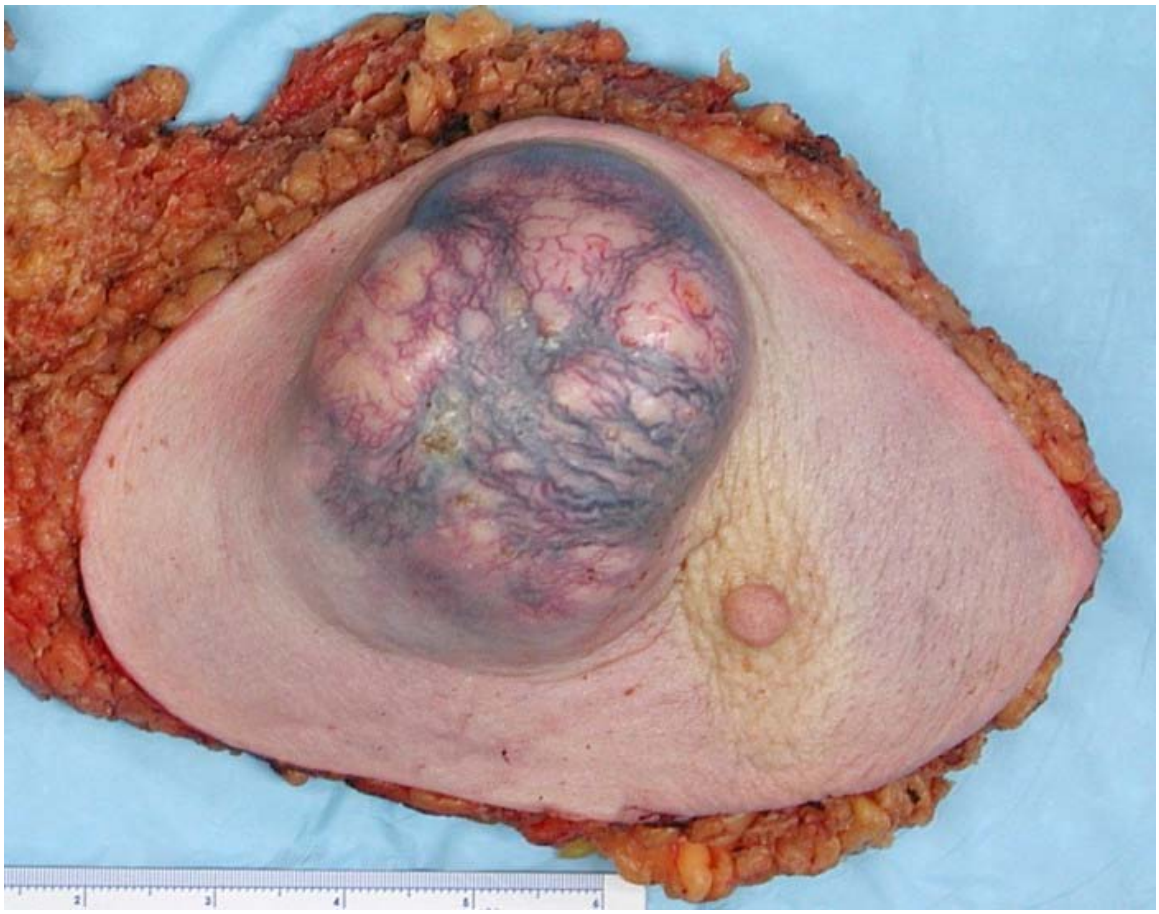
A cancer may be suspected for a variety of reasons, but the definitive diagnosis of most malignancies must be confirmed by histological examination of the cancerous cells by a pathologist. Tissue can be obtained from a biopsy or surgery. Many biopsies (such as those of the skin, breast or liver) can be done in a doctor's office. Biopsies of other organs are performed under anesthesia and require surgery in an operating room.

The tissue diagnosis given by the pathologist indicates the type of cell that is proliferating, its histological grade, genetic abnormalities, and other features of the tumor. Together, this information is useful to evaluate the prognosis of the patient and to choose the best treatment. Cytogenetics and immunohistochemistry are other types of testing that the pathologist may perform on the tissue specimen. These tests may provide information about the molecular changes (such as mutations, fusion genes, and numerical chromosome changes) that has happened in the cancer cells, and may thus also indicate the future behavior of the cancer (prognosis) and best treatment.

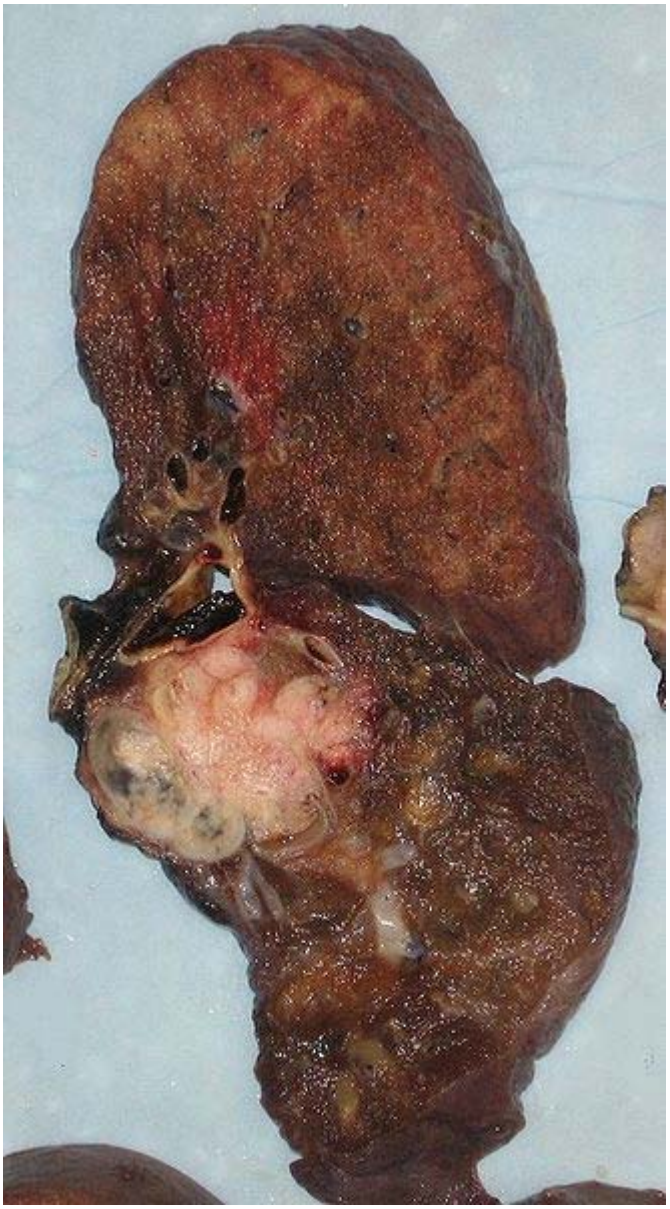


An invasive colorectal carcinoma (top center) in a colectomy specimen

An invasive ductal carcinoma of the breast (pale area at the center) surrounded by spikes of whitish scar tissue in the surrounding yellow fatty tissue.

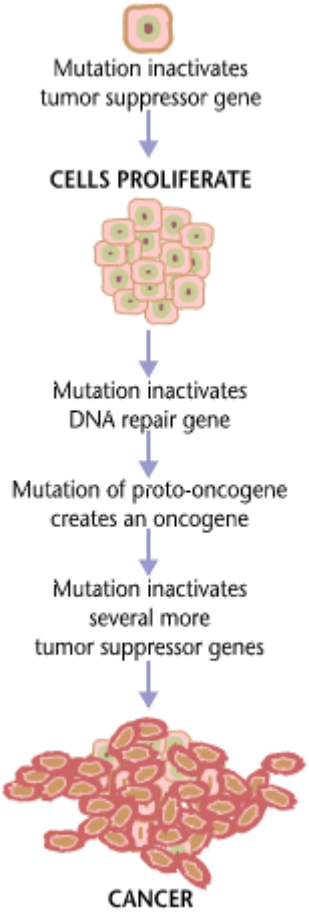


A large invasive ductal carcinoma in a mastectomy specimen



A squamous cell carcinoma (the whitish tumor) near the bronchi in a lung specimen

## *Pathophysiology*




Cancers are caused by a series of mutations. Each mutation alters the behavior of the cell somewhat.

Cancer is fundamentally a disease of failure of regulation of tissue growth. In order for a normal cell to transform into a cancer cell, the genes which regulate cell growth and differentiation must be altered.

The affected genes are divided into two broad categories. Oncogenes are genes which promote cell growth and reproduction. Tumor suppressor genes are genes which inhibit cell division and survival. Malignant transformation can occur through the formation of novel oncogenes, the inappropriate over-expression of normal oncogenes, or by the under-expression or disabling of tumor suppressor genes. Typically, changes in *many* genes are required to transform a normal cell into a cancer cell.

Genetic changes can occur at different levels and by different mechanisms. The gain or loss of an entire chromosome can occur through errors in mitosis. More common are mutations, which are changes in the nucleotide sequence of genomic DNA.

Large-scale mutations involve the deletion or gain of a portion of a chromosome. Genomic amplification occurs when a cell gains many copies (often 20 or more) of a small chromosomal locus, usually containing one or more oncogenes and adjacent genetic material. Translocation occurs when two separate chromosomal regions become abnormally fused, often at a characteristic location. A well-known example of this is the Philadelphia chromosome, or translocation of chromosomes 9 and 22, which occurs in chronic myelogenous leukemia, and results in production of the BCR-abl fusion protein, an oncogenic tyrosine kinase.

Small-scale mutations include point mutations, deletions, and insertions, which may occur in the promoter region of a gene and affect its expression, or may occur in the gene's coding sequence and alter the function or stability of its protein product. Disruption of a single gene may also result from integration of genomic material from a DNA virus or retrovirus, and resulting in the expression of *viral* oncogenes in the affected cell and its descendants.

Replication of the enormous amount of data contained within the DNA of living cells will probabilistically result in some errors (mutations). Complex error correction and prevention is built into the process, and safeguards the cell against cancer. If significant error occurs, the damaged cell can "self destruct" through programmed cell death, termed apoptosis. If the error control processes fail, then the mutations will survive and be passed along to daughter cells.

Some environments make errors more likely to arise and propagate. Such environments can include the presence of disruptive substances called carcinogens, repeated physical injury, heat, ionising radiation, or hypoxia (see causes, below).

The errors which cause cancer are *self-amplifying* and *compounding*, for example:

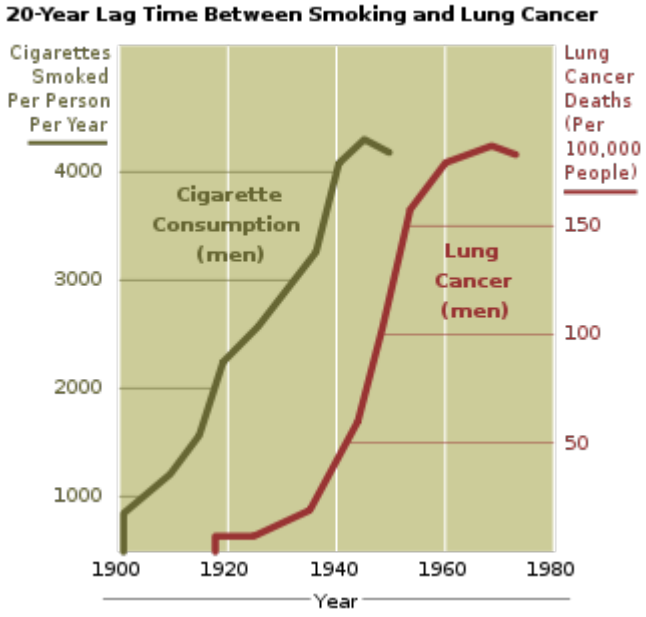
- A mutation in the error-correcting machinery of a cell might cause that cell and its children to accumulate errors more rapidly
- A further mutation in an oncogene might cause the cell to reproduce more rapidly and more frequently than its normal counterparts.
- A further mutation may cause loss of a tumour suppressor gene, disrupting the apoptosis signalling pathway and resulting in the cell becoming immortal.
- A further mutation in signaling machinery of the cell might send error-causing signals to nearby cells

The transformation of normal cell into cancer is akin to a chain reaction caused by initial errors, which compound into more severe errors, each progressively allowing the cell to escape the controls that limit normal tissue growth. This rebellion-like scenario becomes an undesirable survival of the fittest, where the driving forces of evolution work against the body's design and enforcement of order. Once cancer has begun to develop, this ognoing process, termed *clonal evolution* drives progression towards more invasive stages.

## *Causes*

Cancers are primarily an environmental disease with 90-95% of cases due to environmental factors and 5-10% due to genetics. "Environmental", as used by cancer researchers, means any cause that is not genetic, and includes everything from natural sunlight to industrial pollution to viruses to behavioral choices to old age. Most environmental causes, such as naturally occurring background radiation, are not modifiable or controllable. Common environmental factors that lead to cancer death include: tobacco (25-30% of deaths), diet and obesity (30-35%), infections (15-20%), radiation (both ionizing and non ionizing), stress, lack of physical activity, and environmental pollutants.

### Chemicals




The incidence of lung cancer is highly correlated with smoking

Cancer pathogenesis is traceable back to DNA mutations that impact cell growth and metastasis. Substances that cause DNA mutations are known as mutagens, and mutagens that cause cancers are known as carcinogens. Particular substances have been linked to specific types of cancer. Tobacco smoking is associated with many forms of cancer, and causes 90% of lung cancer.

Many mutagens are also carcinogens, but some carcinogens are not mutagens. Alcohol is an example of a chemical carcinogen that is not a mutagen. Such chemicals may promote cancers through stimulating the rate of cell division. Faster rates of replication leaves less time for repair enzymes to repair damaged DNA during DNA replication, increasing the likelihood of a mutation.

Decades of research has demonstrated the link between tobacco use and cancer in the lung, larynx, head, neck, stomach, bladder, kidney, oesophagus and pancreas. Tobacco smoke contains over fifty known carcinogens, including nitrosamines and polycyclic aromatic hydrocarbons. Tobacco is responsible for about one in three of all cancer deaths in the developed world, and about one in five worldwide. Lung cancer death rates in the United States have mirrored smoking patterns, with increases in smoking followed by dramatic increases in lung cancer death rates and, more recently, decreases in smoking followed by decreases in lung cancer death rates in men. However, the numbers of smokers worldwide is still rising, leading to what some organizations have described as the *tobacco epidemic*.

Cancer related to one's occupation is believed to represent between 2-20% of all cases. Every year, at least 200,000 people die worldwide from cancer related to their workplace. Currently, most cancer deaths caused by occupational risk factors occur in the developed world. It is estimated that approximately 20,000 cancer deaths and 40,000 new cases of cancer each year in the U.S. are attributable to occupation. Millions of workers run the risk of developing cancers such as lung cancer and mesothelioma from inhaling asbestos fibers and tobacco smoke, or leukemia from exposure to benzene at their workplaces.

## Physical carcinogens

Some substances cause cancer primarily through their physical, rather than chemical, effects on cells.

A prominent example of this is prolonged exposure to asbestos fibers. Asbestos is a naturally occurring, fibrous rock that causes mesothelioma, a type of lung cancer. Other substances in this category include both naturally occurring and synthetic asbestos-like fibers, such as wollastonite, attapulgite, glass wool, and rock wool, are believed to have similar effects.

Nonfibrous particulate materials that cause cancer include powdered metallic cobalt and nickel, and crystalline silica (quartz, cristobalite, and tridymite).

Usually, physical carcinogens must get inside the body (such as through inhaling tiny pieces) and require years of exposure to develop cancer.

## Radiation

Sources of ionizing radiation, such as radon gas, can cause cancer. Radiation can cause cancer in most parts of the body, in all animals, and at any age, although radiation-induced solid tumors usually take 10–15 years, and up to 40 years, to become clinically manifest, and radiation-induced leukemias typically require 2–10 years to appear. Some people, such as those with nevoid basal cell carcinoma syndrome or retinoblastoma, are more susceptible than average to developing cancer from radiation exposure. Children and adolescents are twice as likely to develop radiation-induced leukemia as adults; radiation exposure before birth has ten times the effect. Ionizing radiation is not a

particularly strong mutagen. Residential exposure to radon gas, for example, has similar cancer risks as passive smoking. Low-dose exposures, such as living near a nuclear power plant, are generally believed to have no or very little effect on cancer development. Radiation is a more potent source of cancer when it is combined with other cancer-causing agents, such as radon gas exposure plus smoking tobacco.

Unlike chemical or physical triggers for cancer, ionizing radiation hits molecules within cells randomly. If it happens to strike a chromosome, it can break the chromosome, result in an abnormal number of chromosomes, inactivate one or more genes in the part of the chromosome that it hit, delete parts of the DNA sequence, cause chromosome translocations, or cause other types of chromosome abnormalities. Major damage normally results in the cell dying, but smaller damage may leave a stable, partly functional cell that may be capable of proliferating and developing into cancer, especially if tumor suppressor genes were damaged by the radiation. Three independent stages appear to be involved in the creation of cancer with ionizing radiation: morphological changes to the cell, acquiring cellular immortality (losing normal, life-limiting cell regulatory processes), and adaptations that favor formation of a tumor. Even if the radiation particle does not strike the DNA directly, it triggers responses from cells that indirectly increase the likelihood of mutations.

Medical use of ionizing radiation is a growing source of radiation-induced cancers. Ionizing radiation may be used to treat other cancers, but this may, in some cases, induce a second form of cancer. It is also used in some kinds of medical imaging. One report estimates that approximately 29,000 future cancers could be related to the approximately 70 million CT scans performed in the US in 2007. It is estimated that 0.4% of current cancers in the United States are due to CTs performed in the past and that this may increase to as high as 1.5-2% with 2007 rates of CT usage.

Prolonged exposure to ultraviolet radiation from the sun can lead to melanoma and other skin malignancies. Clear evidence establishes ultraviolet radiation, especially the medium wave UVB, as the cause of most non-melanoma skin cancers, which are the most common forms of cancer in the world.

Non-ionizing radio frequency radiation from mobile phones, electric power transmission, and other similar sources has also been proposed as a cause of cancer, but there is currently little established evidence of such a link.

## Infection

Some cancers can be caused by infection. This is especially true in animals such as birds, but also in humans, with infections responsible for up to 20% of human cancers worldwide.

Viruses are the most common infectious agents that cause cancer. A virus that can cause cancer is called an *oncovirus*. These include human papillomavirus (cervical carcinoma), Epstein-Barr virus (B-cell lymphoproliferative disease and nasopharyngeal carcinoma),

Kaposi's sarcoma herpesvirus (Kaposi's Sarcoma and primary effusion lymphomas), hepatitis B and hepatitis C viruses (hepatocellular carcinoma), and Human T-cell leukemia virus-1 (T-cell leukemias). Bacterial infection may also increase the risk of cancer, as seen in Helicobacter pylori-induced gastric carcinoma. Parasitic infections strongly associated with cancer include *Schistosoma haematobium* (squamous cell carcinoma of the bladder) and the liver flukes, *Opisthorchis viverrini* and *Clonorchis sinensis* (cholangiocarcinoma).

## Viruses

According to some authors, viruses are one of the most important risks factor for cancer development in humans, second only to tobacco use.

There are two types of cancers caused by viruses: *acutely transforming* or *slowly transforming* cancers. In acutely transforming viruses, the virus carries an overactive oncogene, and the infected cell becomes cancerous as soon as the overactive viral gene is expressed. In contrast, in slowly transforming viruses, the virus genome is inserted near a previously existing proto-oncogene in the genome of the infected cell. The virus causes overexpression of that proto-oncogene, which typically induces uncontrolled cell division. Because the virus' genes might not insert near enough to a proto-oncogene to trigger the cancerous changes, and, even if optimally located, it might take some time to become activated, slowly transforming viruses usually cause tumors much longer after infection than the acutely transforming viruses, if at all.

Infection by some hepatitis viruses, especially hepatitis B and hepatitis C, can induce a chronic viral infection that leads to liver cancer in about 1 in 200 of people infected with hepatitis B each year (more in Asia, fewer in North America), and in about 1 in 45 of people infected with hepatitis C each year. People with chronic hepatitis B infection are more than 200 times more likely to develop liver cancer than uninfected people. Liver cirrhosis, whether from chronic viral hepatitis infection or alcohol abuse or some other cause, is independently associated with the development of liver cancer, and the combination of cirrhosis and viral hepatitis presents the highest risk of liver cancer development. Because chronic viral hepatitis is so common, and liver cancer so deadly, liver cancer is one of the most common causes of cancer-related deaths in the world, and is especially common in East Asia and parts of sub-Sarahan Africa.

Human papillomaviruses (HPV) are another particularly common cancer-causing virus. HPV is well-known for causing genital warts and essentially all cases of cervical cancer, but it can also infect and cause cancer in several other parts of the body, including the larynx, lining of the mouth, nose, and throat, anus, and esophagus. The Papanicolaou smear ("Pap" smear) is a widely used cancer screening test for cervical cancer. DNA-based tests to identify the virus are also available.

Herpesviruses are a third group of common cancer-causing viruses. Two types of herpesviruses have been associated with cancer: the Epstein-Barr virus (EBV) and human herpesvirus 8 (HHV-8). EBV appears to cause all nonkeratinizing nasopharyngeal

carcinomas and some cases of lymphoma, including Burkitt's lymphoma—the association is especially strong in Africa—and Hodgkin's disease. EBV has also been found in a variety of other types of cancer cells, although its role in causing these other cancers is not well established. HHV-8 causes all cases of Kaposi's sarcoma, and has been found in some cases of a cancer-related condition called Castleman's disease. Studies involving other kinds of cancer, particularly prostate cancer, have been inconsistent. Both of these herpesviruses are commonly found in cancerous cells of primary effusion lymphoma. Herpesviruses also cause cancer in animals, especially leukemias and lymphomas.

HIV does not directly cause cancer, but it is associated with a number of malignancies, especially Kaposi's sarcoma, non-Hodgkin's lymphoma, anal cancer and cervical cancer. Kaposi's sarcoma is caused by human herpesvirus 8. AIDS-related cases of anal cancer and cervical cancer are commonly caused by human papillomavirus. After HIV destroys the immune system, the body is no longer able to control these viruses, and the infections manifest as cancer. Certain other immune deficiency states (e.g. common variable immunodeficiency and IgA deficiency) are also associated with increased risk of malignancy.

## Bacterial infections

In addition to viruses, certain kinds of bacteria can cause some cancers. The most prominent example is the link between chronic infection of the wall of the stomach with *Helicobacter pylori* and gastric cancer. Although only a minority of those infected with *Helicobacter* go on to develop cancer, since this bacterial infection is quite common, it may be responsible for most of these cancers.

## Parasites

The parasites that cause schistosomiasis (bilharzia), especially *S. haematobium*, can cause bladder cancer and cancer at other sites. Inflammation triggered by the worm's eggs appears to be the mechanism by which squamous cell carcinoma of the bladder is caused. In Asia, infection by *S. japonicum* is associated with colorectal cancer.

Distomiasis, caused by parasitic liver flukes, is associated with cholangiocarcinoma (cancer of the bile duct) in East Asia.

Malaria is associated with Burkitt's lymphoma in Africa, especially when present in combination with Epstein-Barr virus, although it is unclear whether it is causative.

Parasites are also a significant cause of cancer in animals. *Cysticercus fasciolaris*, the larval form of the common tapeworm of the cat, *Taenia taeniaformis*, causes cancer in rats. *Spirocerca lupi* is associated with esophageal cancer in dogs, at least within the southern United States.

## Heredity

Less than 0.3% of the population are carriers of a genetic mutation which has a large effect on cancer risk. They cause less than 3-10% of all cancer. Some of these syndromes include:

- certain inherited mutations in the genes *BRCA1* and *BRCA2* with a more than 75% risk of breast cancer and ovarian cancer
- tumors of various endocrine organs in multiple endocrine neoplasia (MEN types 1, 2a, 2b)
- Li-Fraumeni syndrome (various tumors such as osteosarcoma, breast cancer, soft tissue sarcoma, brain tumors) due to mutations of p53
- Turcot syndrome (brain tumors and colonic polyposis)
- Familial adenomatous polyposis an inherited mutation of the *APC* gene that leads to early onset of colon carcinoma.
- Hereditary nonpolyposis colorectal cancer (HNPCC, also known as Lynch syndrome) can include familial cases of colon cancer, uterine cancer, gastric cancer, and ovarian cancer, without a preponderance of colon polyps.
- Retinoblastoma, when occurring in young children, is due to a hereditary mutation in the retinoblastoma gene.
- Down syndrome patients, who have an extra chromosome 21, are known to develop malignancies such as leukemia and testicular cancer, though the reasons for this difference are not well understood.

## Hormones

Some hormones cause cancer, primarily by encouraging cell proliferation. Hormones are an important cause of sex-related cancers such as cancer of the breast, endometrium, prostate, ovary, and testis, and also of thyroid cancer and bone cancer.

An individual's hormone levels are mostly determined genetically, so this may at least partly explains the presence of some cancers that run in families that do not seem to have any cancer-causing genes. For example, the daughters of women who have breast cancer have significantly higher levels of estrogen and progesterone that the daughters of women without breast cancer. These higher hormone levels may explain why these women have higher risk of breast cancer, even in the absence of a breast-cancer gene. Similarly, men of African ancestry have significantly higher levels of testosterone than men of European ancestry, and have a correspondingly much higher level of prostate cancer. Men of Asian ancestry, with the lowest levels of testosterone-activating androstanediol glucuronide, have the lowest levels of prostate cancer.

However, non-genetic factors are also relevant: Obese people have higher levels of some hormones associated with cancer, and a higher rate of those cancers. Women who take hormone replacement therapy have a higher risk of developing cancers associated with those hormones. On the other hand, people who exercise far more than average have lower levels of these hormones, and lower risk of cancer.

Osteosarcoma (bone cancer) may be caused by growth hormones.

Some treatments and prevention approaches leverage this cause by artificially reducing hormone levels, and thus discouraging hormone-sensitive cancers.

## Physical trauma and inflammation

Physical trauma resulting in cancer is relatively rare. Claims that breaking bone resulted in bone cancer, for example, have never been proven. Similarly, physical trauma is not accepted as a cause for cervical cancer, breast cancer, or brain cancer.

One accepted source is frequent, long-term application of hot objects to the body. It is possible that repeated burns on the same part of the body, such as those produced by kanger and kairo heaters (charcoal hand warmers), may produce skin cancer, especially if carcinogenic chemicals are also present. Frequently drinking scalding hot tea may produce esophageal cancer.

Generally, it is believed that the cancer arises, or a pre-existing cancer is encouraged, during the process of repairing the trauma, rather than the cancer being caused directly by the trauma. However, repeated injuries to the same tissues might promote excessive cell proliferation, which could then increase the odds of a cancerous mutation. There is no evidence that inflammation itself causes cancer.

## Other

Excepting the rare transmissions that occur with pregnancies and only a marginal few organ donors, cancer is generally not a transmissible disease. The main reason for this is tissue graft rejection caused by MHC incompatibility. In humans and other vertebrates, the immune system uses MHC antigens to differentiate between "self" and "non-self" cells because these antigens are different from person to person. When non-self antigens are encountered, the immune system reacts against the appropriate cell. Such reactions may protect against tumour cell engraftment by eliminating implanted cells. In the United States, approximately 3,500 pregnant women have a malignancy annually, and transplacental transmission of acute leukaemia, lymphoma, melanoma and carcinoma from mother to fetus has been observed. The development of donor-derived tumors from organ transplants is exceedingly rare. The main cause of organ transplant associated tumors seems to be malignant melanoma, that was undetected at the time of organ harvest. though other cases exist In fact, cancer from one organism will usually grow in another organism of that species, as long as they share the same histocompatibility genes, proven using mice; however this would never happen in a real-world setting except as described above.

In non-humans, a few types of transmissible cancer have been described, wherein the cancer spreads between animals by transmission of the tumor cells themselves. This phenomenon is seen in dogs with Sticker's sarcoma, also known as canine transmissible venereal tumor, as well as devil facial tumour disease in Tasmanian devils.

## *Prevention*

Cancer prevention is defined as active measures to decrease the incidence of cancer. The vast majority of cancer risk factors are environmental or lifestyle-related, thus cancer is largely a preventable disease. Greater than 30% of cancer is preventable via avoiding risk factors including: tobacco, overweight or obesity, low fruit and vegetable intake, physical inactivity, alcohol, sexually transmitted infection, air pollution.

Examples of modifiable cancer risk factors include alcohol consumption (associated with increased risk of oral, esophageal, breast, and other cancers), smoking (80% of women with lung cancer have smoked in the past, and 90% of men), physical inactivity (associated with increased risk of colon, breast, and possibly other cancers), and being overweight / obese (associated with colon, breast, endometrial, and possibly other cancers). Based on epidemiologic evidence, it is now thought that avoiding excessive alcohol consumption may contribute to reductions in risk of certain cancers; however, compared with tobacco exposure, the magnitude of effect is modest or small and the strength of evidence is often weaker. Other lifestyle and environmental factors known to affect cancer risk (either beneficially or detrimentally) include certain sexually transmitted diseases (such as those conveyed by the human papillomavirus), the use of exogenous hormones, exposure to ionizing radiation and ultraviolet radiation from the sun or from tanning beds, and certain occupational and chemical exposures.

### Diet and obesity

The consensus on diet and cancer is that obesity increases the risk of developing cancer. Particular dietary practices often explain differences in cancer incidence in different countries (e.g. gastric cancer is more common in Japan, while colon cancer is more common in the United States. In this example the preceding consideration of Haplogroups are excluded). Studies have shown that immigrants develop the risk of their new country, often within one generation, suggesting a substantial link between diet and cancer. Whether reducing obesity in a population also reduces cancer incidence is unknown.

However some studies have found that consuming lots of fruits and vegetables has little if any effect on preventing cancer.

Proposed dietary interventions for primary cancer risk reduction generally gain support from epidemiological association studies. Examples of such studies include reports that reduced meat consumption is associated with decreased risk of colon cancer, and reports that consumption of coffee is associated with a reduced risk of liver cancer. Studies have linked consumption of grilled meat to an increased risk of stomach cancer, colon cancer, breast cancer, and pancreatic cancer, a phenomenon which could be due to the presence of carcinogens such as 2-amino-1-methyl-6-phenylimidazo (4,5-b) pyridine (PhIP) in foods cooked at high temperatures.

A recent study analysed the correlation between many factors and cancer and concluded that the major contributory dietary factor was animal protein, whereas plant protein did not have an effect. Animal studies confirmed the mechanism by showing that reducing the proportion of animal protein switched off both the initiation and promotion stages.

A 2005 secondary prevention study showed that consumption of a plant-based diet and lifestyle changes resulted in a reduction in cancer markers in a group of men with prostate cancer who were using no conventional treatments at the time. These results were amplified by a 2006 study. Over 2,400 women were studied, half randomly assigned to a normal diet, the other half assigned to a diet containing less than 20% calories from fat. The women on the low fat diet were found to have a markedly lower risk of breast cancer recurrence, in the interim report of December, 2006.

Recent studies have also demonstrated potential links between some forms of cancer and high consumption of refined sugars and other simple carbohydrates. Although the degree of correlation and the degree of causality is still debated, some organizations have in fact begun to recommend reducing intake of refined sugars and starches as part of their cancer prevention regimens.

10 recommendations to reduce the risk of developing cancer, including the following dietary guidelines: (1) reducing intake of foods and drinks that promote weight gain, namely energy-dense foods and sugary drinks, (2) eating mostly foods of plant origin, (3) limiting intake of red meat and avoiding processed meat, (4) limiting consumption of alcoholic beverages, and (5) reducing intake of salt and avoiding mouldy cereals (grains) or pulses (legumes).

## Medication

The concept that medications could be used to prevent cancer is an attractive one, and many high-quality clinical trials support the use of such chemoprevention in defined circumstances.

Aspirin has been found to reduce the risk of death from cancer.

Daily use of tamoxifen, a selective estrogen receptor modulator (SERM), typically for 5 years, has been demonstrated to reduce the risk of developing breast cancer in high-risk women by about 50%. Raloxifene also a SERM; has been shown to reduce the risk of breast cancer in high-risk women equally as well as tamoxifen. It had fewer side effects than tamoxifen, though it did permit more DCIS to form.

Finasteride, a 5-alpha-reductase inhibitor, has been shown to lower the risk of prostate cancer, though it seems to mostly prevent low-grade tumors. The effect of COX-2 inhibitors such as rofecoxib and celecoxib upon the risk of colon polyps have been studied in familial adenomatous polyposis patients and in the general population. In both groups, there were significant reductions in colon polyp incidence, but this came at the price of increased cardiovascular toxicity.

Vitamins have not been found to be effective at preventing cancer, although low levels of vitamin D are correlated with increased cancer risk. Whether this relationship is causal and vitamin D supplementation is protective is yet to be determined. Beta-carotene supplementation has been found to increase slightly, but not significantly, risks of lung cancer. Folic acid supplementation has not been found effective in preventing colon cancer and may increase colon polyps.

### Vaccination

Vaccines have been developed that prevent some infection by some viruses that are associated with cancer, and therapeutic vaccines are in development to stimulate an immune response against cancer-specific epitopes. Human papillomavirus vaccine (Gardasil and Cervarix) decreases the risk of developing cervical cancer. The hepatitis B vaccine prevents infection with hepatitis B virus and thus decreases the risk of liver cancer.

Advances in cancer research have made a vaccine designed to prevent cancers available. In 2006, the U.S. Food and Drug Administration approved a human papilloma virus vaccine, called Gardasil. The vaccine protects against 6,11,16,18 strains of HPV, which together cause 70% of cervical cancers and 90% of genital warts. It also lists vaginal and vulvar cancers as being protected. In March 2007, the US Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) officially recommended that females aged 11–12 receive the vaccine, and indicated that females as young as age 9 and as old as age 26 are also candidates for immunization. There is a second vaccine from Cervarix which protects against the more dangerous HPV 16,18 strains only. In 2009, Gardasil was approved for protection against genital warts. In 2010, the Gardasil vaccine was approved for protection against anal cancer for males and reviewers stated there was no anatomical, histological or physiological anal differences between the genders so females would also be protected.

## *Screening*

Unlike diagnosis efforts prompted by symptoms and medical signs, cancer screening involves efforts to detect cancer after it has formed, but before any noticeable symptoms appear. This may involve physical examination, blood or urine tests, or medical imaging.

Cancer screening is not currently possible for some types of cancers, and even when tests are available, they are not recommended to everyone. *Universal screening* or *mass screening* involves screening everyone. *Selective screening* identifies people who are known to be at higher risk of developing cancer, such as people with a family history of cancer.

Several factors are considered to determine whether the benefits of screening outweigh the risks and the costs of screening. These factors include:

- **Possible harms from the screening test:** Some types of screening tests, such as X-ray images, expose the body to potentially harmful ionizing radiation. There is a small chance that the radiation in the test could cause a new cancer in a healthy person. Screening mammography, used to detect breast cancer, is not recommended to men or to young women because they are more likely to be harmed by the test than to benefit from it. Other tests, such as a skin check for skin cancer, have no significant risk of harm to the patient. A test that has high potential harms is only recommended when the benefits are also high.
- **The likelihood of the test correctly identifying cancer:** If the test is not *sensitive*, then it may miss cancers. If the test is not *specific*, then it may wrongly indicate cancer in a healthy person. All cancer screening tests produce both false positives and false negatives, and most produce more false positives. Experts consider the rate of errors when making recommendations about which test, if any, to use. A test may work better in some populations than others. The positive predictive value is a calculation of the likelihood that a positive test result actually represents cancer in a given individual, based on the results of people with similar risk factors.
- **The likelihood of cancer being present:** Screening is not normally useful for rare cancers. It is rarely done for young people, since cancer is largely a disease found in people over the age of 50. Countries often focus their screening recommendations on the major forms of treatable cancer found in their population. For example, the United States recommends universal screening for colon cancer, which is common in the US, but not for stomach cancer, which is less common; by contrast, Japan recommends screening for stomach cancer, but not colon cancer, which is rarer in Japan. Screening recommendations depend on the individual's risk, with high-risk people receiving earlier and more frequent screening than low-risk people.
- **Possible harms from follow-up procedures:** If the screening test is positive, further diagnostic testing is normally done, such as a biopsy of the tissue. If the test produces many false positives, then many people will undergo needless medical procedures, some of which may be dangerous.
- **Whether suitable treatment is available and appropriate:** Screening is discouraged if no effective treatment is available. When effective and suitable treatment is not available, then diagnosis of a fatal disease produces significant mental and emotional harms. For example, routine screening for cancer is typically not appropriate in a very frail elderly person, because the treatment for any cancer that is detected might kill the patient.
- **Whether early detection improves treatment outcomes:** Even when treatment is available, sometimes early detection does not improve the outcome. If the treatment result is the same as if the screening had not been done, then the only screening program does is increase the length of time the person lived with the knowledge that he had cancer. This phenomenon is called lead-time bias. A useful screening program reduces the number of years of potential life lost (longer lives) and disability-adjusted life years lost (longer healthy lives).
- **Whether the cancer will ever need treatment:** Diagnosis of a cancer in a person who will never be harmed by the cancer is called *overdiagnosis*. Overdiagnosis is

most common among older people with slow-growing cancers. Concerns about overdiagnosis are common for breast and prostate cancer.
- **Whether the test is acceptable to the patients:** If a screening test is too burdensome, such as requiring too much time, too much pain, or culturally unacceptable behaviors, then people will refuse to participate.
- **How much the test costs:** Some expert bodies, such as the U.S. Preventive Services Task Force, completely ignore the question of money. Most, however, include a cost-effectiveness analysis that, all else being equal, favors less expensive tests over more expensive tests, and attempt to balance the cost of the screening program against the benefits of using those funds for other health programs. These analyses usually include the total cost of the screening program to the healthcare system, such as ordering the test, performing the test, reporting the results, and biopsies for suspicious results, but not usually the costs to the individual, such as for time taken away from employment.

### Recommendations

The U.S. Preventive Services Task Force (USPSTF) strongly recommends cervical cancer screening in those who are sexually active and have a cervix at least until the age of 65. They recommend mammography for breast cancer screening every two years for those 50–74 years old, however do not recommend either breast self-examination or clinical breast examination. Colorectal cancer screening is recommended via fecal occult blood testing, sigmoidoscopy, or colonoscopy starting at age 50 until age 75. There is insufficient evidence to recommend for or against screening for skin cancer, oral cancer, lung cancer, or prostate cancer in men under 75. Routine screening is not recommended for bladder cancer, testicular cancer, ovarian cancer, pancreatic cancer, or prostate cancer in men over 75. A 2009 Cochrane review came to slightly different conclusions with respect to breast cancer screening stating that routine mammography may do more harm than good.

### Genetic testing

| Gene | Cancer types |
|---|---|
| BRCA1, BRCA2 | Breast, ovarian, pancreatic |
| HNPCC, MLH1, MSH2, MSH6, PMS1, PMS2 | Colon, uterine, small bowel, stomach, urinary tract |

Genetic testing for individuals at high-risk of certain cancers is recommended. Carriers of these mutations may than undergo enhanced surveillance, chemoprevention, or preventative surgery to reduce their subsequent risk.

## *Management*

Many management options for cancer exist including: chemotherapy, radiation therapy, surgery, immunotherapy, monoclonal antibody therapy and other methods. Which

treatments are used depends upon the type of cancer, the location and grade of the tumor, and the stage of the disease, as well as the general state of a person's health.

Complete removal of the cancer without damage to the rest of the body is the goal of treatment for most cancers. Sometimes this can be accomplished by surgery, but the propensity of cancers to invade adjacent tissue or to spread to distant sites by microscopic metastasis often limits its effectiveness. Surgery often required the removal of a wide surgical margin or a free margin. The width of the free margin depends on the type of the cancer, the method of removal (CCPDMA, Mohs surgery, POMA, etc.). The margin can be as little as 1 mm for basal cell cancer using CCPDMA or Mohs surgery, to several centimeters for aggressive cancers. The effectiveness of chemotherapy is often limited by toxicity to other tissues in the body. Radiation can also cause damage to normal tissue.

Because cancer is a class of diseases, it is unlikely that there will ever be a single "cure for cancer" any more than there will be a single treatment for all infectious diseases. Angiogenesis inhibitors were once thought to have potential as a "silver bullet" treatment applicable to many types of cancer, but this has not been the case in practice.

Experimental cancer treatments are treatments that are being studied to see whether they work. Typically, these are studied in clinical trials to compare the proposed treatment to the best existing treatment. They may be entirely new treatments, or they may be treatments that have been used successfully in one type of cancer, and are now being tested to see whether they are effective in another type.

Alternative cancer treatments are treatments used by alternative medicine practitioners. These include mind–body interventions, herbal preparations, massage, electrical devices, and strict dietary regimens. Alternative cancer treatments are ineffective at killing cancer cells. Some are dangerous, but more are harmless or provide the patient with a degree of physical or emotional comfort. Alternative cancer treatment has also been a fertile field for hoaxes aimed at stripping desperate patients of their money.

## *Prognosis*

Cancer has a reputation as a deadly disease. Taken as a whole, about half of patients receiving treatment for invasive cancer (excluding carcinoma in situ and non-melanoma skin cancers) die from cancer or its treatment. However, the survival rates vary dramatically by type of cancer, with the range running from basically all patients surviving to almost no patients surviving.

Patients who receive a long-term remission or permanent cure may have physical and emotional complications from the disease and its treatment. Surgery may have amputated body parts or removed internal organs, or the cancer may have damaged delicate structures, like the part of the ear that is responsible for the sense of balance; in some cases, this requires extensive physical rehabilitation or occupational therapy so that the patient can walk or engage in other activities of daily living. Chemo brain is a usually short-term cognitive impairment associated with some treatments. Cancer-related fatigue

usually resolves shortly after the end of treatment, but may be lifelong. Cancer-related pain may require ongoing treatment. Younger patients may be unable to have children. Some patients may be anxious or psychologically traumatized as a result of their experience of the diagnosis or treatment.

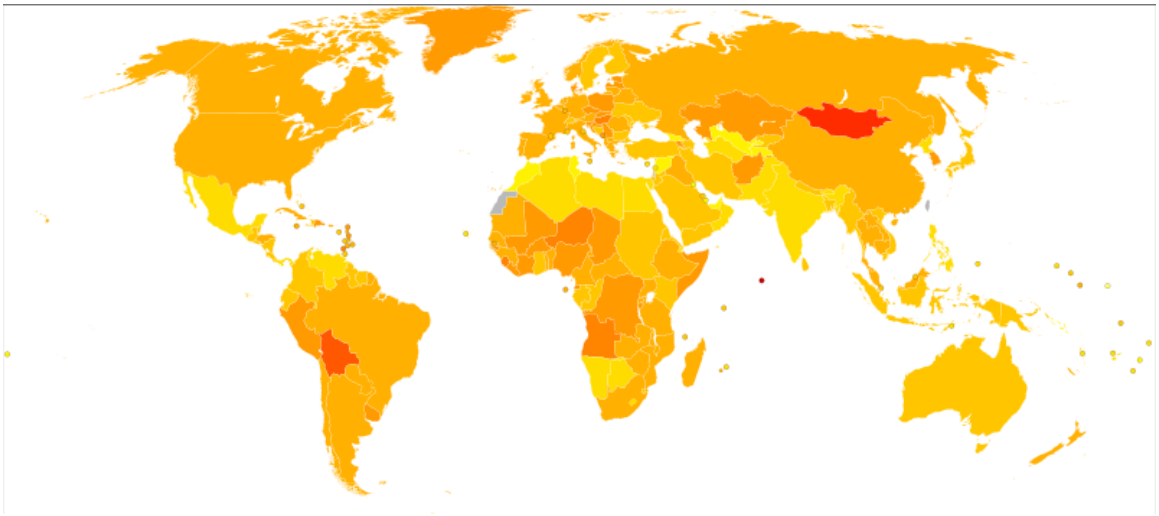
Survivors generally need to have regular medical screenings to ensure that the cancer has not returned, to manage any ongoing cancer-related conditions, and to screen for new cancers. Cancer survivors, even when permanently cured of the first cancer, have approximately double the normal risk of developing another primary cancer. Some advocates have promoted "survivor care plans"—written documents detailing the diagnosis, all previous treatment, and all recommended cancer screening and other care requirements for the future—as a way of organizing the extensive medical information that survivors and their future healthcare providers need.

Progressive and disseminated malignant disease harms the cancer patient's quality of life, and some cancer treatments, including common forms of chemotherapy, have severe side effects. In the advanced stages of cancer, many patients need extensive care, affecting family members and friends. Palliative care aims to improve the patient's immediate quality of life, regardless of whether further treatment is undertaken. Hospice programs assist patients similarly, especially when a terminally ill patient has rejected further treatment aimed at curing the cancer. Both styles of service offer home health nursing and respite care.

Predicting either short-term or long-term survival is difficult and depends on many factors. The most important factors are the particular kind of cancer and the patient's age and overall health. Medically frail patients with many comorbidities have lower survival rates than otherwise healthy patients. A centenarian is unlikely to survive for five years even if the treatment is successful. Patients who report a higher quality of life tend to survive longer. People with lower quality of life may be affected by major depressive disorder and other complications from cancer treatment and/or disease progression that both impairs their quality of life and reduces their quantity of life. Additionally, patients with worse prognoses may be depressed or report a lower quality of life directly because they correctly perceive that their condition is likely to be fatal.

Despite strong social pressure to maintain an upbeat, optimistic attitude or act like a determined "fighter" to "win the battle", personality traits have no connection to survival.

## *Epidemiology*

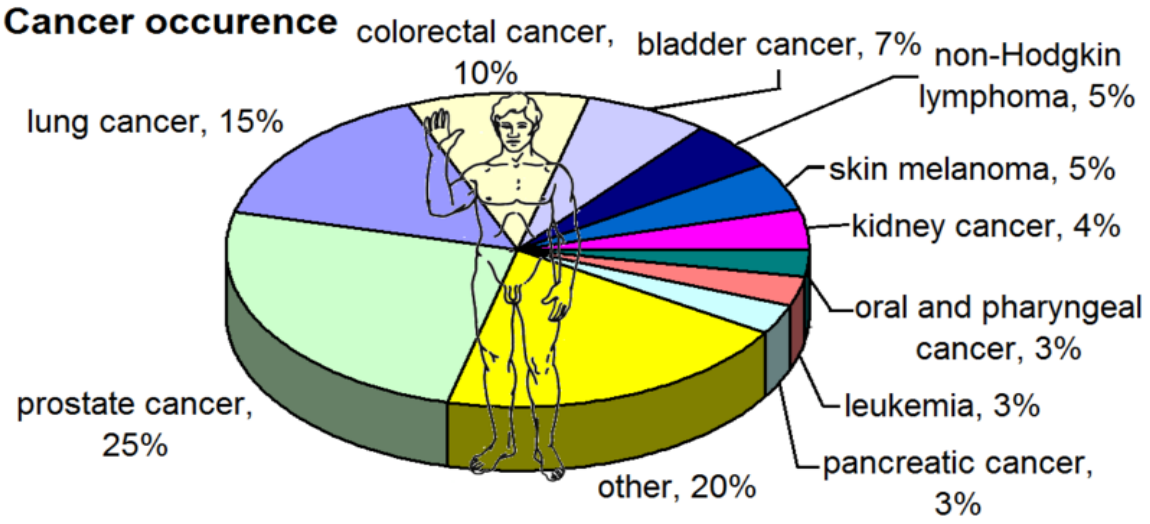


Death rate from malignant cancer per 100,000 inhabitants in 2004.
- no data
- ≤ 55
- 55-80
- 80-105
- 105-130
- 130-155
- 155-180
- 180-205
- 205-230
- 230-255
- 255-280
- 280-305
- ≥ 305

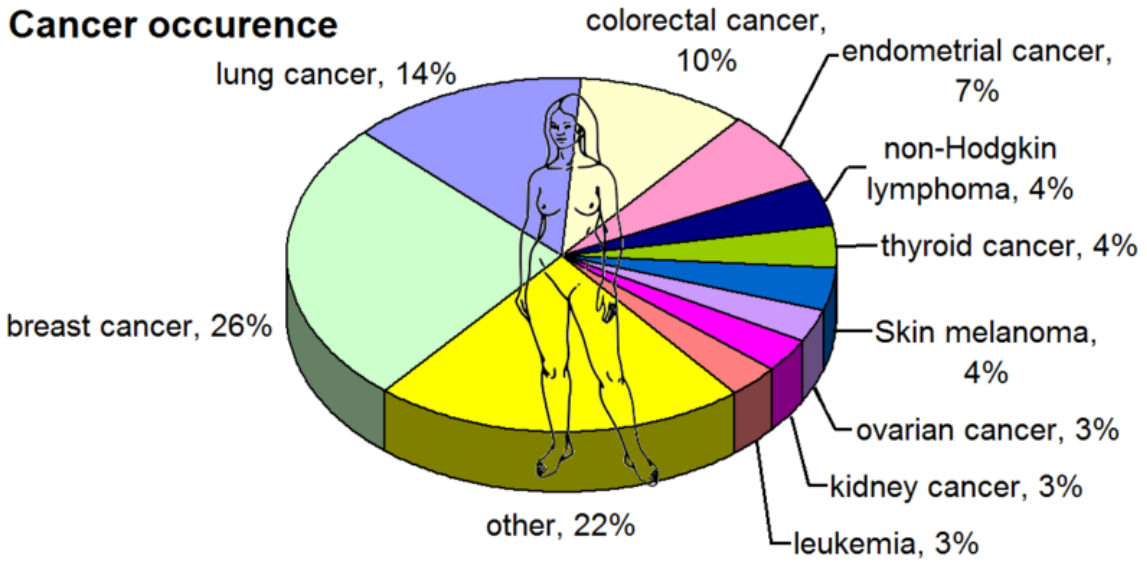
As of 2004, worldwide cancer caused 13% of all deaths (7.4 million). The leading causes were: lung cancer (1.3 million deaths/year), stomach cancer (803,000 deaths), colorectal cancer (639,000 deaths), liver cancer (610,000 deaths), and breast cancer (519,000 deaths). The most significant risk factor is age. According to cancer researcher Robert A. Weinberg, "If we lived long enough, sooner or later we all would get cancer." Essentially all of the increase in cancer rates between ancient times and the beginning of the 20th century in England is due to increased lifespans. Since then, some other factors, especially the increased use of tobacco, have further raised the rates.

In the United States, cancer is responsible for 25% of all deaths with 30% of these from lung cancer. The most commonly occurring cancer in men is prostate cancer (about 25% of new cases) and in women is breast cancer (also about 25%). Cancer can occur in children and adolescents, but it is uncommon (about 150 cases per million in the U.S.), with leukemia the most common. In the first year of life the incidence is about 230 cases per million in the U.S., with the most common being neuroblastoma.

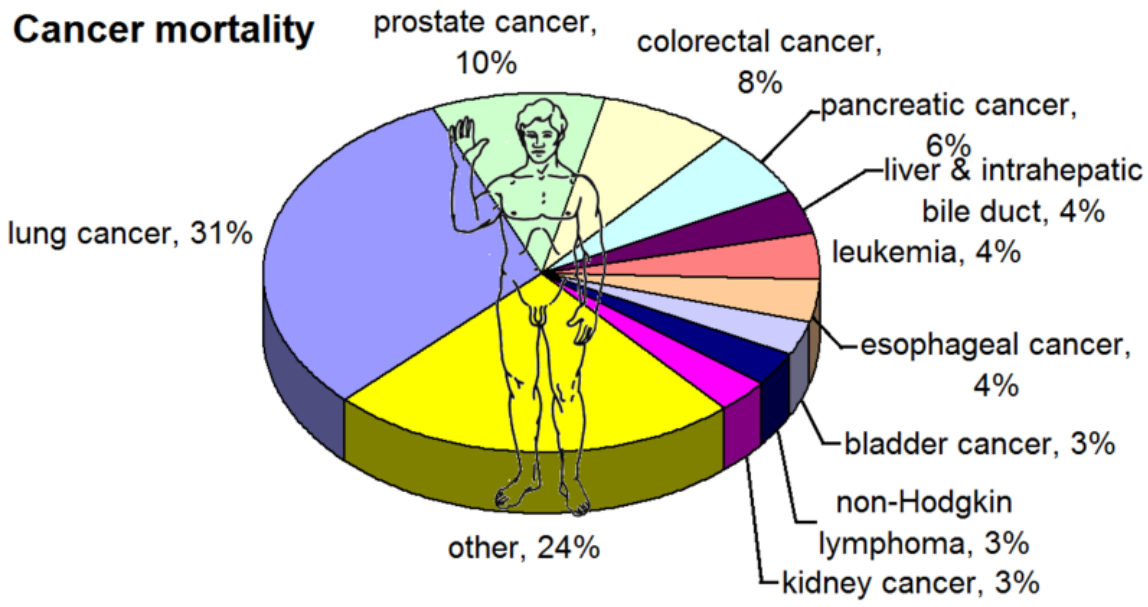
In the developed world, one in three people will develop cancer during their lifetimes. If *all* cancer patients survived and cancer occurred *randomly*, the lifetime odds of developing a second primary cancer would be one in nine. However, cancer survivors have an increased risk of developing a second primary cancer, and the odds are about two in nine. About half of these second primaries can be attributed to the normal one-in-nine risk associated with random chance. The increased risk is believed to be primarily due to the same risk factors that produced the first cancer (such as the person's genetic profile, alcohol and tobacco use, obesity, and environmental exposures), and partly due to the treatment for the first cancer, which typically includes mutagenic chemotherapeutic drugs or radiation. Cancer survivors may also be more likely to comply with recommended screening, and thus may be more likely than average to detect cancers.



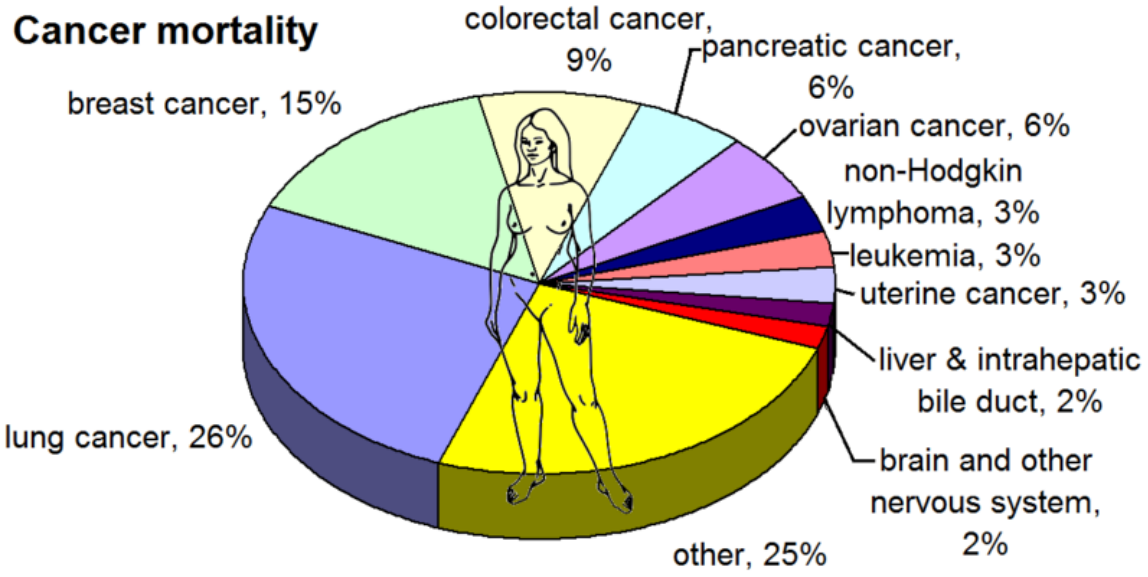

Most common cancers in US males, by occurrence




in US females, by occurrence




in US males, by mortality




in US females, by mortality

## *History*

Hippocrates (ca. 460 BC – ca. 370 BC) described several kinds of cancers, referring to them with the Greek word *carcinos* (crab or crayfish), among others. This name comes from the appearance of the cut surface of a solid malignant tumour, with "the veins stretched on all sides as the animal the crab has its feet, whence it derives its name". Since it was against Greek tradition to open the body, Hippocrates only described and made drawings of outwardly visible tumors on the skin, nose, and breasts. Treatment was

based on the humor theory of four bodily fluids (black and yellow bile, blood, and phlegm). According to the patient's humor, treatment consisted of diet, blood-letting, and/or laxatives. Through the centuries it was discovered that cancer could occur anywhere in the body, but humor-theory based treatment remained popular until the 19th century with the discovery of cells.

Engraving with two views of a Dutch woman who had a tumor removed from her neck in 1689.

Celsus (ca. 25 BC - 50 AD) translated *carcinos* into the Latin *cancer*, also meaning crab. Galen (2nd century AD) called benign tumours *oncos*, Greek for swelling, reserving Hippocrates' *carcinos* for malignant tumours. He later added the suffix *-oma*, Greek for swelling, giving the name *carcinoma*.

The oldest known description and surgical treatment of cancer was discovered in Egypt and dates back to approximately 1600 BC. The Papyrus describes 8 cases of ulcers of the breast that were treated by cauterization, with a tool called "the fire drill." The writing says about the disease, "There is no treatment."

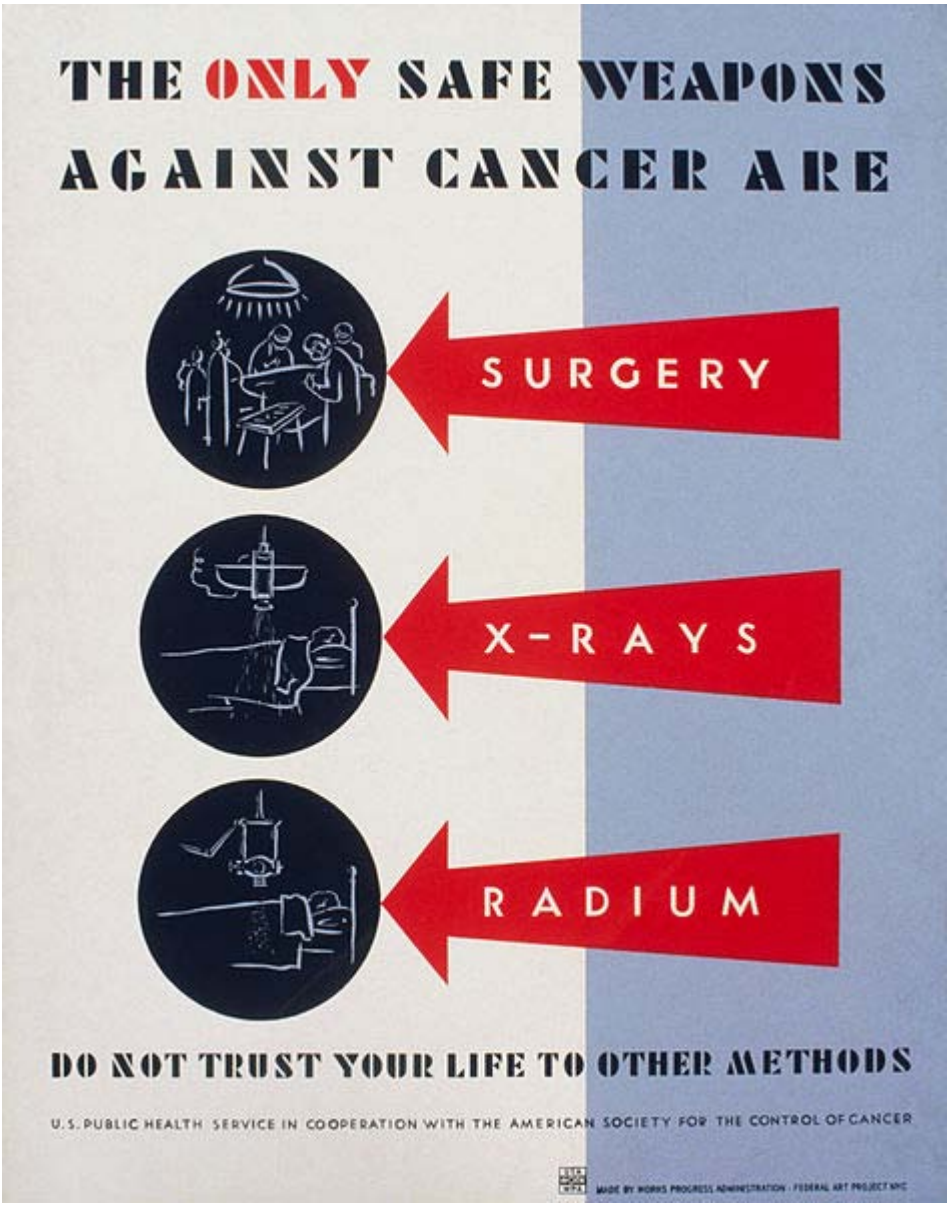
Another very early surgical treatment for cancer was described in the 1020s by Avicenna (Ibn Sina) in *The Canon of Medicine*. He stated that the excision should be radical and that all diseased tissue should be removed, which included the use of amputation or the removal of veins running in the direction of the tumor. He also recommended the use of cauterization for the area treated if necessary.

In the 16th and 17th centuries, it became more acceptable for doctors to dissect bodies to discover the cause of death. The German professor Wilhelm Fabry believed that breast cancer was caused by a milk clot in a mammary duct. The Dutch professor Francois de la Boe Sylvius, a follower of Descartes, believed that all disease was the outcome of chemical processes, and that acidic lymph fluid was the cause of cancer. His contemporary Nicolaes Tulp believed that cancer was a poison that slowly spreads, and concluded that it was contagious.

The first cause of cancer was identified by British surgeon Percivall Pott, who discovered in 1775 that cancer of the scrotum was a common disease among chimney sweeps. The work of other individual physicians led to various insights, but when physicians started working together they could make firmer conclusions.

With the widespread use of the microscope in the 18th century, it was discovered that the 'cancer poison' spread from the primary tumor through the lymph nodes to other sites ("metastasis"). This view of the disease was first formulated by the English surgeon Campbell De Morgan between 1871 and 1874. The use of surgery to treat cancer had poor results due to problems with hygiene. The renowned Scottish surgeon Alexander Monro saw only 2 breast tumor patients out of 60 surviving surgery for two years. In the 19th century, asepsis improved surgical hygiene and as the survival statistics went up, surgical removal of the tumor became the primary treatment for cancer. With the exception of William Coley who in the late 19th century felt that the rate of cure after surgery had been higher *before* asepsis (and who injected bacteria into tumors with mixed results), cancer treatment became dependent on the individual art of the surgeon at removing a tumor. During the same period, the idea that the body was made up of various tissues, that in turn were made up of millions of cells, laid rest the humor-theories about chemical imbalances in the body. The age of cellular pathology was born.

The genetic basis of cancer was recognised in 1902 by the German zoologist Theodor Boveri, professor of zoology at Munich and later in Würzburg. He discovered a method to generate cells with multiple copies of the centrosome, a structure he discovered and named. He postulated that chromosomes were distinct and transmitted different inheritance factors. He suggested that mutations of the chromosomes could generate a cell with unlimited growth potential which could be passed onto its descendants. He proposed the existence of cell cycle check points, tumour suppressor genes and oncogenes. He speculated that cancers might be caused or promoted by radiation, physical or chemical insults or by pathogenic microorganisms.




1938 poster identifying surgery, x-rays and radium as the proper treatments for cancer

When Marie Curie and Pierre Curie discovered radiation at the end of the 19th century, they stumbled upon the first effective non-surgical cancer treatment. With radiation also came the first signs of multi-disciplinary approaches to cancer treatment. The surgeon was no longer operating in isolation, but worked together with hospital radiologists to help patients. The complications in communication this brought, along with the necessity of the patient's treatment in a hospital facility rather than at home, also created a parallel process of compiling patient data into hospital files, which in turn led to the first statistical patient studies.

A founding paper of cancer epidemiology was the work of Janet Lane-Claypon, who published a comparative study in 1926 of 500 breast cancer cases and 500 control

patients of the same background and lifestyle for the British Ministry of Health. Her ground-breaking work on cancer epidemiology was carried on by Richard Doll and Austin Bradford Hill, who published "Lung Cancer and Other Causes of Death In Relation to Smoking. A Second Report on the Mortality of British Doctors" followed in 1956 (otherwise known as the British doctors study). Richard Doll left the London Medical Research Center (MRC), to start the Oxford unit for Cancer epidemiology in 1968. With the use of computers, the unit was the first to compile large amounts of cancer data. Modern epidemiological methods are closely linked to current concepts of disease and public health policy. Over the past 50 years, great efforts have been spent on gathering data across medical practise, hospital, provincial, state, and even country boundaries to study the interdependence of environmental and cultural factors on cancer incidence.

Cancer patient treatment and studies were restricted to individual physicians' practices until World War II, when medical research centers discovered that there were large international differences in disease incidence. This insight drove national public health bodies to make it possible to compile health data across practises and hospitals, a process that many countries do today. The Japanese medical community observed that the bone marrow of victims of the atomic bombings of Hiroshima and Nagasaki was completely destroyed. They concluded that diseased bone marrow could also be destroyed with radiation, and this led to the discovery of bone marrow transplants for leukemia. Since World War II, trends in cancer treatment are to improve on a micro-level the existing treatment methods, standardize them, and globalize them to find cures through epidemiology and international partnerships.

## *Society and culture*

While many diseases (such as heart failure) may have a worse prognosis than most cases of cancer, it is the subject of widespread fear and taboos. Euphemisms, once "a long illness", and now informally as "the big C", provide distance and soothe superstitions. This deep belief that cancer is necessarily a difficult and usually deadly disease is reflected in the systems chosen by society to compile cancer statistics: the most common form of cancer—non-melanoma skin cancers, accounting for about one-third of all cancer cases worldwide, but very few deaths—are excluded from cancer statistics specifically because they are easily treated and almost always cured, often in a single, short, outpatient procedure.

Cancer is regarded as a disease that must be "fought" to end the "civil insurrection"; a War on Cancer has been declared. Military metaphors are particularly common in descriptions of cancer's human effects, and they emphasize both the parlous state of the affected individual's health and the need for the individual to take immediate, decisive actions himself, rather than to delay, to ignore, or to rely entirely on others caring for him. The military metaphors also help rationalize radical, destructive treatments.

In the 1970s, a relatively popular alternative cancer treatment was a specialized form of talk therapy, based on the idea that cancer was caused by a bad attitude. People with a

"cancer personality"—depressed, repressed, self-loathing, and afraid to express their emotions—were believed to have manifested cancer through subconscious desire. Some psychotherapists said that treatment to change the patient's outlook on life would cure the cancer. Among other effects, this belief allows society to blame the victim for having caused the cancer (by "wanting" it) or having metaphysically prevented its cure (by not becoming a sufficiently happy, fearless, and loving person). It also increases patients' anxiety, as they incorrectly believe that natural emotions of sadness, anger or fear shorten their lives. The idea was excoriated by the notoriously outspoken Susan Sontag, who published *Illness as Metaphor* while recovering from treatment for breast cancer in 1978.

Although the original idea is now generally regarded as nonsense, the idea partly persists in a reduced form with a widespread, but incorrect, belief that deliberately cultivating a habit of positive thinking will increase survival. This notion is particularly strong in breast cancer culture.

## *Research*

Cancer research is the intense scientific effort to understand disease processes and discover possible therapies.

Research about cancer causes focusses on the following issues:

- Agents (e.g. viruses) and events (e.g. mutations) which cause or facilitate genetic changes in cells destined to become cancer.
- The precise nature of the genetic damage, and the genes which are affected by it.
- The consequences of those genetic changes on the biology of the cell, both in generating the defining properties of a cancer cell, and in facilitating additional genetic events which lead to further progression of the cancer.

The improved understanding of molecular biology and cellular biology due to cancer research has led to a number of new, effective treatments for cancer since President Nixon declared "War on Cancer" in 1971. Since 1971 the United States has invested over $200 billion on cancer research; that total includes money invested by public and private sectors and foundations. Despite this substantial investment, the country has seen a five percent decrease in the cancer death rate (adjusting for size and age of the population) between 1950 and 2005.

Leading cancer research organizations and projects include the American Association for Cancer Research, the American Cancer Society (ACS), the American Society of Clinical Oncology, the European Organisation for Research and Treatment of Cancer, the National Cancer Institute, the National Comprehensive Cancer Network, and The Cancer Genome Atlas project at the NCI.