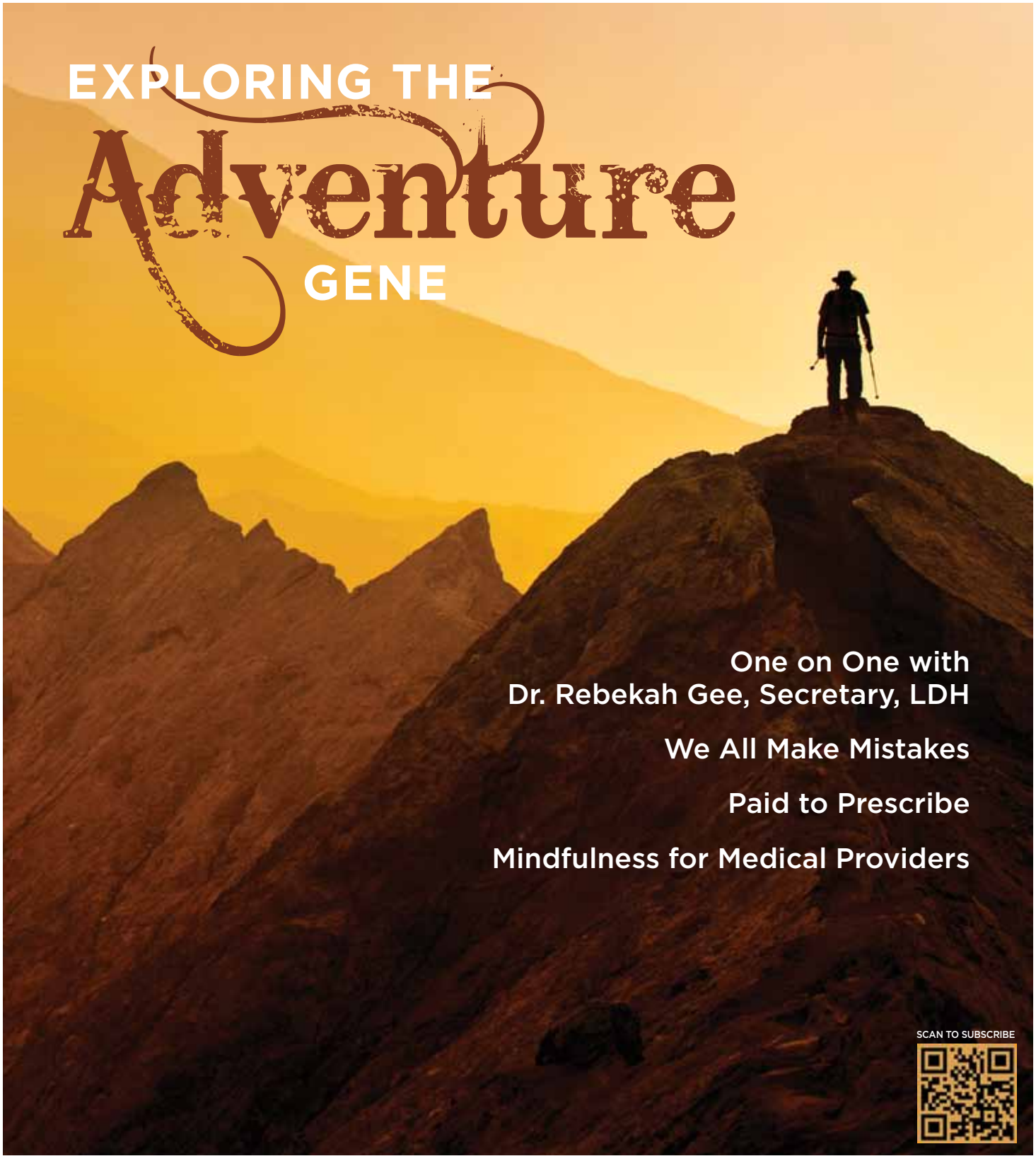
HEALTHCARE JOURNAL of New Orleans

JULY / AUGUST 2016 | HEALTHCAREJOURNALNO.COM | $8



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July / August 2016 | Vol. 5, No. 4

All Who Wander Are Not Lost...

BUT THEY MAY BE GENETICALLY DRIVEN

By **Claudia S. Copeland, PhD**

Summer is here, and for many Louisianans, this means the happy anticipation of leaving the steamy sidewalks of New Orleans for a holiday break. Many of us will leave town for some leisurely downtime in beach resorts, European hotels, or cozy country B&Bs. Others, though, will head for rugged adventures in the mountains or the sea, or fly to faraway countries, relishing the challenge of day to day living in an unknown land–foreign language, unfamiliar infrastructure and customs, exotic food and culture. When you think of summer vacation, do you look forward to rest and relaxation or do you relish the chance for travel and adventure? Molecular geneticists are uncovering evidence that at least part of your preference may lie in your genes.

c. 150

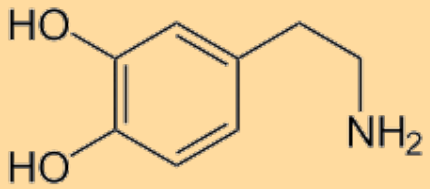
Galen practices and teaches pharmacy and medicine in Rome. His principles of preparing and compounding medicines become the standard for 1,500 years.

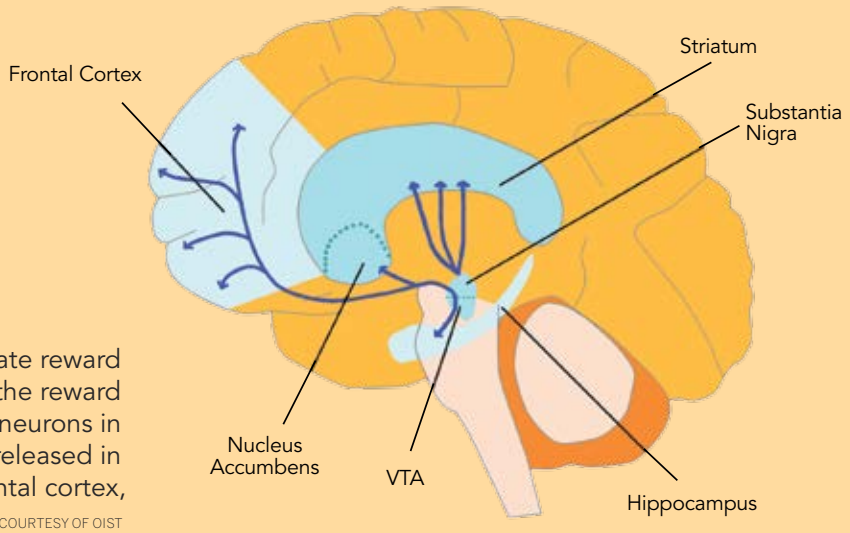
c. 400-1100

In Europe, monks gather and grow herbs to prepare medicines and treat the sick.

c. 700

Arabs open the first apothecary shops in Baghdad. The tradition travels with the Muslims to Europe.





In the brain, dopamine helps regulate reward and body movement. As part of the reward pathway, dopamine is produced by neurons in the ventral tegmental area (VTA) and released in the nucleus accumbens and the prefrontal cortex, leading to the feeling of pleasure. IMAGE COURTESY OF OIST

The idea of a genetic basis for this kind of "adventure drive" launched into mainstream biology in 1996, with two studies published side-by-side in *Nature Genetics*. Together, they described a gene variant correlated with a personality trait known as Novelty Seeking, a trait associated with impulsive and exploratory behavior. The gene they looked at encodes a specific type of dopamine receptor, called dopamine receptor D4 or DRD4. Dopamine is involved in reward-motivated behavior, as well as muscle movement and cognitive functions like attention and learning. As with any neurotransmitter, its effect will differ depending on the post-synaptic neuron—the neuron that receives the dopamine "message"—and the networks this neuron activates. In terms of human experience, the eventual effect could be a physical movement, a feeling, or a thought (cognition). There are five different types of dopamine receptors, each correlated with different categories of effects. D4 receptors, densely located in basal areas of the brain involved in reward-motivated behavior, have been implicated in addiction, eating disorders, and other disorders involving impulsive behavior, such as pathological gambling.

While the involvement of the D4 receptor in psychological conditions and cognition was well-accepted by the mid-1990s, it was quite a stretch to say that any single gene mutation could affect a personality trait. Personality is complex, governed by a number of factors including non-biological ones, such as childhood environment, and changing ones, such as age. (The novelty-seeking personality trait diminishes with age.) When a specific genetic polymorphism was found to be correlated with this personality trait, the first flurry of activity was, naturally, attempts to replicate or refute the finding. Those attempts, as is often the case when studying complex traits, were conflicting, with some supporting the correlation between D4 variants and novelty seeking, and others finding no evidence of a link. Many findings do support a connection between DRD4 and novelty seeking, but the nature of DRD4's influence on personality is complex; DRD4 is one factor among many that work together to determine the phenotype. Furthermore, while most of the initial studies focused on novelty seeking, there is more to DRD4 variation than an adventurous mindset. Many studies have linked DRD4 variants with novelty-related

"What advantage might a species gain by having a novelty-seeking gene in a minority of its members? One advantage might be invasion of new territory."

novelty seeking

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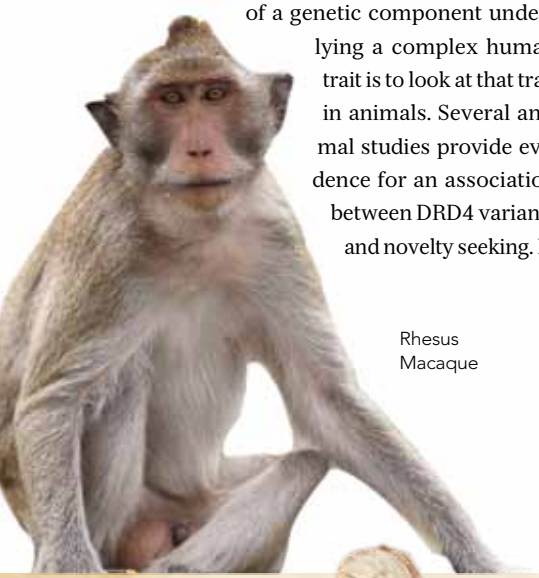
problems like substance abuse and ADHD in children. Other effects are more mysterious, such as preliminary studies suggesting enhanced perception of others' mental states (theory of mind decoding) among depressed patients with DRD4 variants. Still others are perplexing, such as the finding that children with DRD4 variants were more sensitive to loss in negative childhood environments but had more positive psychological responses to loss than normal children when raised in favorable childhood environments. At this stage in time, research on DRD4 in humans is generating many more questions than answers.

One way to obtain a clearer picture of a genetic component underlying a complex human trait is to look at that trait in animals. Several animal studies provide evidence for an association between DRD4 variants and novelty seeking. In 2007, Andrew Fidler and colleagues reported that DRD4 variants in the passarine bird Parus major were associated with early exploratory behavior (EEB), a measurable variable representing the trait of novelty seeking in birds. In Spanish and Portuguese populations of an invasive bird species, ornithologists Mueller et al. set up an experiment in which, after acclimation, they placed a novel object (apple slice or battery) in the birds' cage. Most of the birds avoided the objects, increased their movement, and even appeared to be looking for an escape route, but a few paused, approached the objects and even touched them. Genotyping the birds, variant SNPs of DRD4 accounted for 11-15% of the novelty seeking phenotypes, a significant correlation.



Rhesus Macaque

These bird studies support similar findings in mammals. Japanese researchers Momozawa et al. found DRD4 variants to be correlated with two equine temperament traits, curiosity and vigilance, in 2-year-old thoroughbred horses. Horses with the DRD4 variant had significantly higher scores in curiosity and lower scores in vigilance than horses with normal DRD4 genes. Other equine studies have shown differences in DRD4 profiles in different breeds of horses, and differences according to temperament.

In primates, UCLA researchers Bailey et al. reported that vervet monkeys with variant DRD4 genes were significantly more likely to approach a novel object placed in their cage than monkeys with the normal DRD4 gene. In a free-ranging rhesus macaque population in Puerto Rico, monkeys with the variant DRD4 allele spent less time in proximity to their mothers, avoided other individuals more often, and experienced behavioral restlessness more often than monkeys with the normal DRD4 allele. DRD4 variants have been associated with social impulsivity and activity/impulsivity/inattention in German shepherd and Siberian husky breeds of dogs.

It is intriguing that these DRD4 gene results are seen in such disparate species. The presence of this phenomenon in a broad array of animals supports an evolutionary advantage to such a trait. What advantage might a species gain by having a novelty-seeking gene in a minority of its members?

c. 1000

The pharmaceutical teachings of Ibn Sina, pharmacist, poet, physician, philosopher, and diplomat, are the accepted authority in the West until the 17th century and still are dominant influences in Eastern cultures.

1240

Holy Roman Emperor Frederic II issues a decree by which the professions of physician and apothecary are separated.

1345

The first "pharmacy" opens in London.

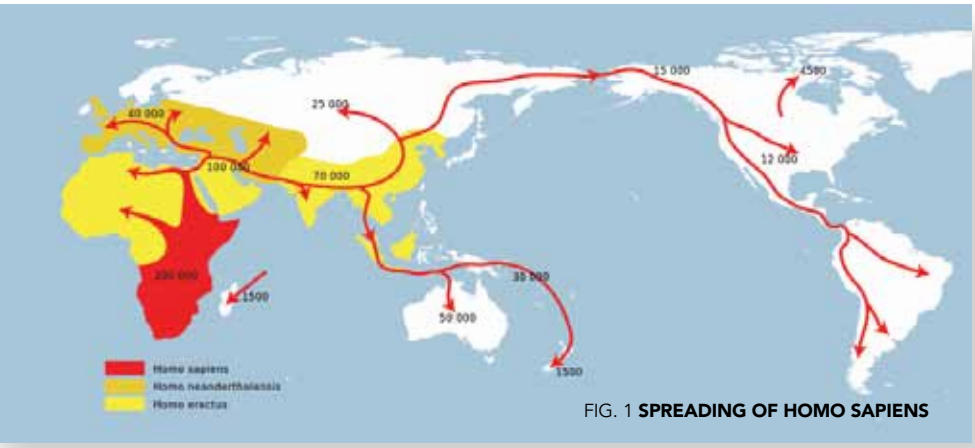
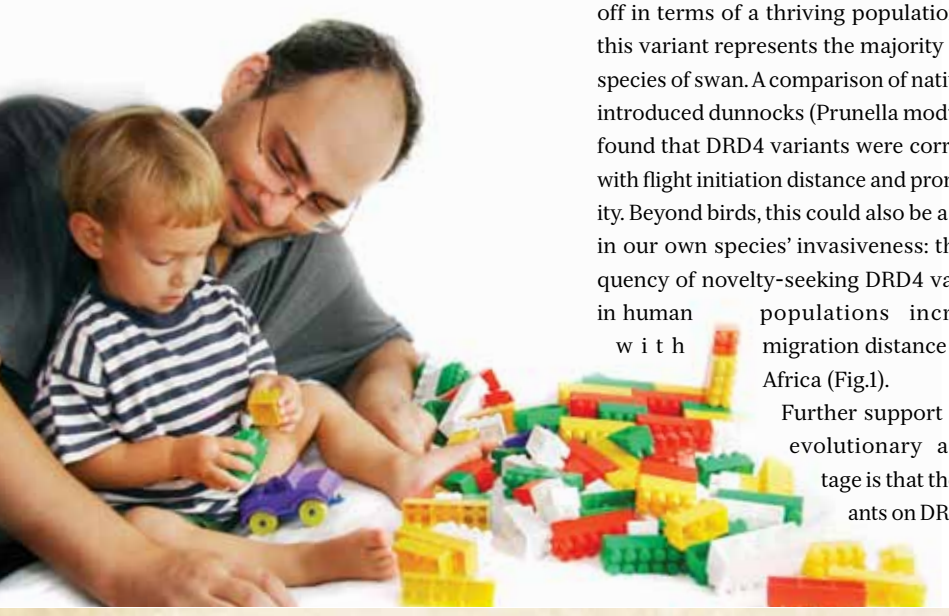


FIG. 1 **SPREADING OF HOMO SAPIENS**

BY NORDNORDWEST (FILE:SPREADING HOMO SAPIENS RU.SVG BY URUTSEG) [PUBLIC DOMAIN], VIA WIKIMEDIA COMMONS

One advantage might be invasion of new territory. While staying in a safe, well-understood environment is a survival advantage on the individual level, it could be to the advantage of populations to have some members with a drive to explore out and colonize new and unknown territory.

Studies of invasive bird populations have found DRD4 variants correlated with bold behavior such as flying longer distances. A recent study of black swans in urban environments found that swans who settled in less-disturbed areas away from humans were three times as likely to possess DRD4 variants associated with wariness (non-novelty seeking). Since swans are supported by humans, exploratory/risk-taking behavior could certainly pay off in terms of a thriving population, and this variant represents the majority in this species of swan. A comparison of native and introduced dunnocks (Prunella modularis) found that DRD4 variants were correlated with flight initiation distance and promiscuity. Beyond birds, this could also be a factor in our own species' invasiveness: the frequency of novelty-seeking DRD4 variants in human populations increases with migration distance out of Africa (Fig.1).



Further support for an evolutionary advantage is that the variants on DRD4 are not all the same—some are repeat lengths, some are different SNPs. In addition, other genes, such as serotonin-related genes, have also been implicated in novelty-seeking. The implication is that different genetic variations can result in novelty-seeking individuals, and that these different genetic variants represent convergent evolution of an advantageous trait on the population level.

So, it looks like novelty-seeking in some members can be beneficial to a population. Still, though, in most populations, the majority of individuals are non-novelty-seeking. Can this type of genetic variant lead to disadvantages? In humans, there are plenty of examples of when it does. One is a correlation with substance abuse, and especially severity of drug dependence. Another is sexual promiscuity. Pathological gambling, poor self-regulation, and ADHD in children have also been associated with novelty-seeking DRD4 variants. As with much research in humans, results are controversial, and any genetic predisposition is one factor in a complex array. Whether or not the genotype of a DRD4 variant might be harmful or helpful in humans largely depends on the individual's other personality traits, as well as environmental factors such as education level.

In one particularly intriguing study, Chi et al. examined the phenomenon of job-changing and how genetics may interact with socioeconomic factors. Previous studies in twins have indicated a clear genetic component to the phenomenon of job-changing frequency. Chi et al. were interested in how early-life environmental factors interact with genetics to shape behavioral phenomena. They looked at the interaction between DRD4 variants and two early-life

1386

Chaucer refers to "farmacies of herbs" in The Knight's Tale to describe medical preparation of plants.

1498

The first official pharmacopoeia is released in Florence.

1600

Apothecaries prepare and dispense medicine but also examine and treat patients, setting them apart from what would be considered a pharmacist. Later they are also granted prescriptive power.

"Rather than trying to "straighten out" a novelty-seeking teenager, realizing that this may be an in-born genetic trait suggests the importance of fostering healthy pursuits that involve curiosity and exploration..."

environmental factors, family socioeconomic status and neighborhood poverty, with respect to job-changing. Citing previous literature on "hobo syndrome"–the tendency for people with personality traits of impulsivity and openness to get a "periodic itch" to move from job to job, this team looked at the possibility that DRD4 variation might modify the effects of environmental factors on job changing. They found that DRD4 variants were associated with two strengthened effects according to childhood environment: a greater frequency of voluntary job changing among people who grew up with high SES (and had more education), and a higher frequency of involuntary job changing among people who had grown up in environments with high neighborhood poverty. This dovetails with emerging, preliminary studies showing stronger susceptibility to the influence of both positive and negative environmental influences among children with DRD4 variants.

While our understanding of the contribution of genetic variation to novelty seeking is still in its infancy, a growing body of research indicates that some people (and animals) seem to be genetically predisposed to crave novelty. How might this insight be useful? Organizational researchers are interested in this phenomenon as it pertains to job placement, and developmental and clinical psychologists are interested in how it relates to clinical conditions such as ADHD.

Perhaps more importantly, on a personal level, if you or someone you know seems to have an irrational craving for novelty, knowing that it may be genetic can be a valuable insight. Rather than wondering why you can't just settle down in life, if you seem to have an in-born drive to explore, prioritizing time and resources for travel or learning new skills could mean the difference between depression and a life of anticipation of adventures on the horizon. For young novelty-seekers, toys that can be constantly changed and made new, like Legos, may be a good way to channel their impulses, along with prioritizing activities like outdoor exploration. Rather than trying to "straighten out" a novelty-seeking teenager, realizing that this may be an in-born genetic trait suggests the importance of fostering healthy pursuits that involve curiosity and exploration, like science, journalism, or exploratory sports like diving. After all, in today's fast-changing world, that novelty-seeking streak that causes so much worry for parents could be a great asset–the difference between being stressed and dismayed by a changing world, or embracing change as an exhilarating challenge, relishing the ride into the uncharted future. ■

1605

Louis Hébert becomes apothecary to New France when he helps de Monts and Champlain build the New World settlement at Port Royal (Nova Scotia, Canada).

1700s

James Oglethorpe, founder of the Georgia colony, backed by the Worshipful Society of Apothecaries of London, launches an effort to identify and transplant beneficial plant species from the tropical colonies to Savannah.

1729

Christopher Marshall, an Irish immigrant, establishes his apothecary shop in Philadelphia. Eventually it is managed by granddaughter Elizabeth, America's first female pharmacist.