**Describe the two main reasons that people respond differently to the same medicine, giving an explanation for your answer in each case and examples for each of your two reasons.**

**Answer:**

Medicines do not have a similar response in all the people, and it act differently in some of the people and or individuals. The effect could be lower or higher; duration may be shorter or longer, and undue effects which can be dangerous too.

There are two main reasons which are expected to cause such variations, i.e., genetic variation (genome) and influences from the environment. Therefore, an individual patient needs personalized medicine for the treatment [1].

A medicine acts on the target inside the human body, and such interactions lead to the generation of effect. Target is generally a human protein and is supposed to interact with medicine and give clinical benefit and or causing toxicity. These proteins are being a product of a single gene which is the key for differentiation via mutation. Genetic variations come by mutation, and it occurs regularly; among them, most are beneficial, and some are harmful.

Due to deviation in the target and as well metabolic profile, thus drug may have variation in the response because of genetic deviation in the patients. Thus, a similar drug with same dose still has different outcome and may not be equally effective in a large number of populations which significantly varying in genetic makeup. Thereby different person need a different therapy approach and it can be utilized studying pharmacogenomics which help in utilizing the drug and its dose [2].

It is known that a human being is having nearly 24,000 genes and 100,000 proteins which comprises of nearly 100,000 amino acids differing in sequencing. Mutations lead the genetic variation, and currently, known mutations are almost 1.000.000. [3].

Receptors or enzymes are targeted by the drugs, which are pretentious in nature, comprising the amino acids and proteins are translated by m-RNA with the help of DNA. Defects in protein synthesis may be caused by a genetic mutation which is because a change in the gene sequence which is responsible for the synthesis of proteins. Such protein may be structurally having variation and may not function properly. There are many diseases which are caused by such genetic variation or mutation like sickle cell anaemia. This disease is caused by mutation in the gene code responsible for the synthesis of hemoglobin. There is a mutation of GAG into GTG code (Figure 1), which results in a change of amino acid 6-Glu (Glutamic acid) into 6-Val (valine). Such change leads to alter the structure of RBCs (Red blood cells), which are attached by Plasmodium

parasite (a malaria-causing parasite), but due to alteration in RBCs led to resistance and would not allow to the entry of parasite [4].

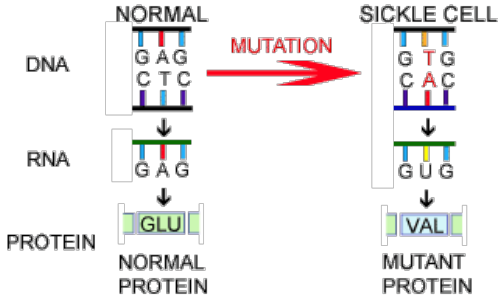
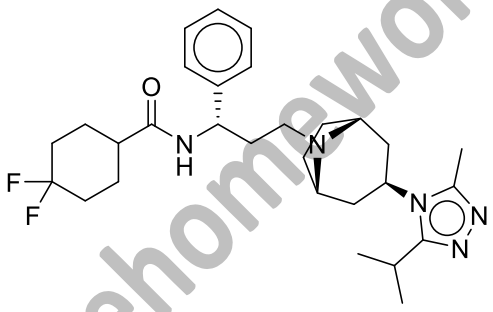



Figure 1: mutation causing Sickle cell anemia (From ref. 5)

The human immune deficiency virus (HIV) causing the AIDS disease is used to enter T cells. CXCR4 facilitates the entry into T cells as co-receptor or WT CCR5 receptor, however mutation of the receptor via CCR5Δ32 (about 1.5%) leading to develop resistance against the access of HIV. Maraviroc was developed and discovered based on that entry point Δ32; it helped in the treatment of HIV infection (Figure 2) via blocking the CCR5 receptor and halts HIV entrance [6].




Maraviroc

Figure 2: Chemical structure of maraviroc

Cytochrome P450s (CYPs) proteins are showed variation due to mutation frequently occurs CYP coding genes. CYPs are functioning to metabolize the drug and different organic molecules; due to frequent mutation, these show polymorphism, which leads to variation in metabolism of drug kinetics in interindividual. Out of different CYPs, CYP2D6 is most commonly involved in drug metabolism, and overall, 25% of drugs are metabolized by this CYP. CYP2D6 also showed polymorphism due to mutation, which affects the drug metabolism kinetics and efficacy, varying the dose.

CYP2D6*3 is one of the gene variations causing the dead enzyme which is observed in 1 to 3% in Caucasians. This will lead to high drug levels in the body and causing the toxicity of such drugs, which remain unmetabolized due to inactive CYO2D6*3. In 10 to 30% of Ethiopians and middle Eastern people have the CYP2D6*2xN type duplication, resulting in overactivation of the enzyme

metabolism. A higher metabolic rate will be led to a low level of drug in the body, and thus drug shows less efficacy.

Almost 30% of Africans were found to have a triple mutation in CYP2D6*17 such as, R296C, T107I, and S486T, which led to enzyme activity lowered and decelerate the metabolism, which may enhance the danger of toxicity [7].

Like morphine-derived codeine is metabolized by CYP2D6 enzyme. Codeine acts as a pain killer and is metabolised into morphine as a more active pain killer metabolite. Morphine is 200 times more potent than codeine (Figure 3). But the activity of metabolising enzyme i.e., CYP2D6 varies in interindividual like some are poor metaboliser CYP2D6 phenotypes, and such persons need more dose of normal metaboliser to produce similar effect [8].

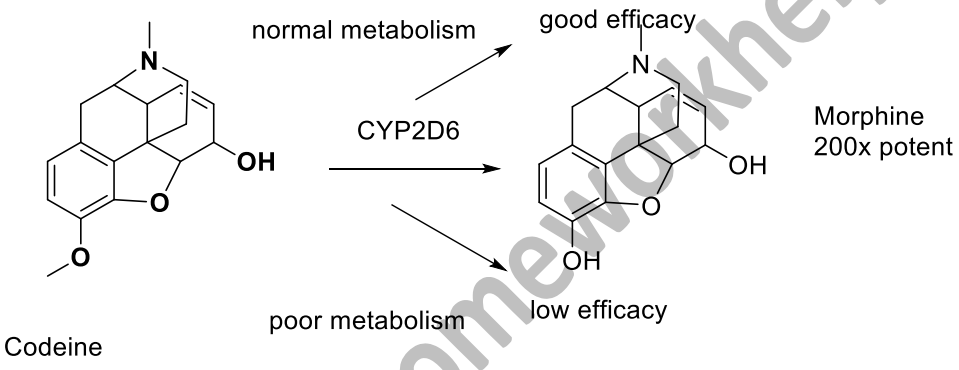



Figure 3: Difference in the metabolism of codeine

There are several environmental factors which also affect the drug efficacy or activity via altering drugs kinetics like absorption, distribution, metabolism, and excretion. Also, these factors may change the interaction of the drug at the binding site. It was observed that the patients' microbiome is significantly influencing the drug reaction via metabolizing enzyme. There are ca 40 trillion microbes in human beings located in different parts and affecting the various activities and variations in them, causing the disease (Figure 4) [9].

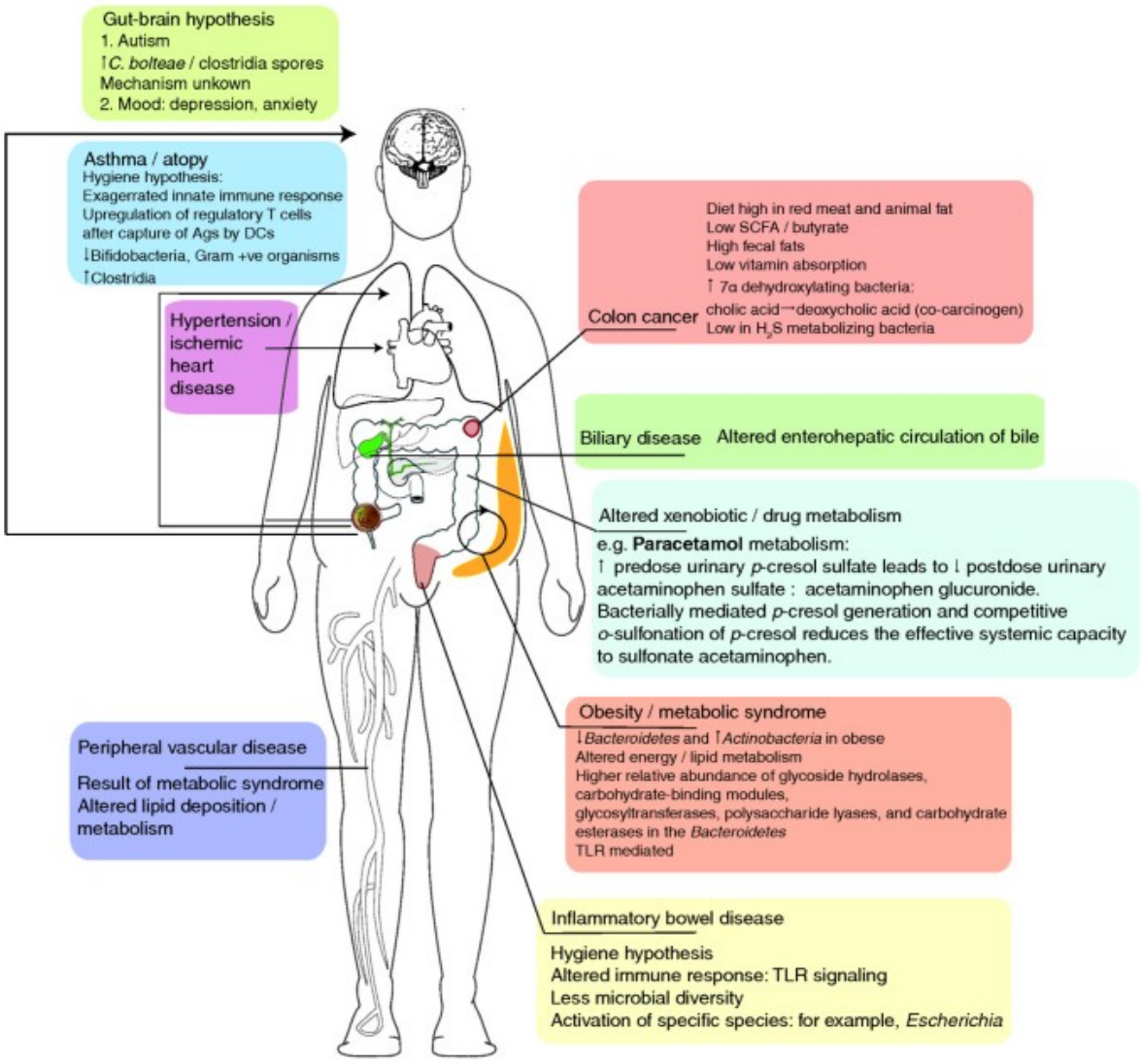



Figure 4: Diseases influenced by gut microbial metabolism (From ref. 9)



Obesity is hugely increased in past 30 years. It is denoted by increased body mass index (BMI) > 30 kg/m$^2$). It is observed that it is not merely controlled by genetic factors but also via the microbiome.

It is found that the obese people having different species of microbiome (bacteria) than lean people, and this significantly affect the metabolism. They are involved ed in extraction of more energy from same food. An increased absorption of nutrients via thin mucus line of the gut is also causing obesity.

Roux-en-Y gastric bypass (RYGB) lead to lower down the absorption of nutrient in human and in mice and significantly causing in weight reduction. This is leading to significantly change in microbiome involve in fatty acid production. After bypass surgery an increase in Escherichia and Akkermansia (nearly 10,000-fold) while decreasing Chlostridiales bacteria was observed. A 1000

more *Akkermansia municiphila* was found in lean mice than genetically obese ob-ob mice. Thus, supporting the fact that obesity is also caused by microbiome [10].

In another example where some microbe may lead to cause serious concern like *C. difficilie* is found in normal human gut microbiome. But after antibiotic treatment, different good microbes get wiped out, and levels of *C. difficilie* raised significantly. It gets colonized in the gut, taking over the other bacteria and causing fever and diarrhea [11].

Few examples are discussed below, which give insight into the microbiome.

Gut microbiotas improve the metabolism of sulfasalazine, which is a codrug and inactive. Thus gut microbioata causing the activation of sulfasalazine in to mesalazine and sulfapyridine via azo reductase enzyme produced by them. This drug is used to treat rheumatoid arthritis, ulcerative colitis, and Crohn's disease. (Figure 5) [12].

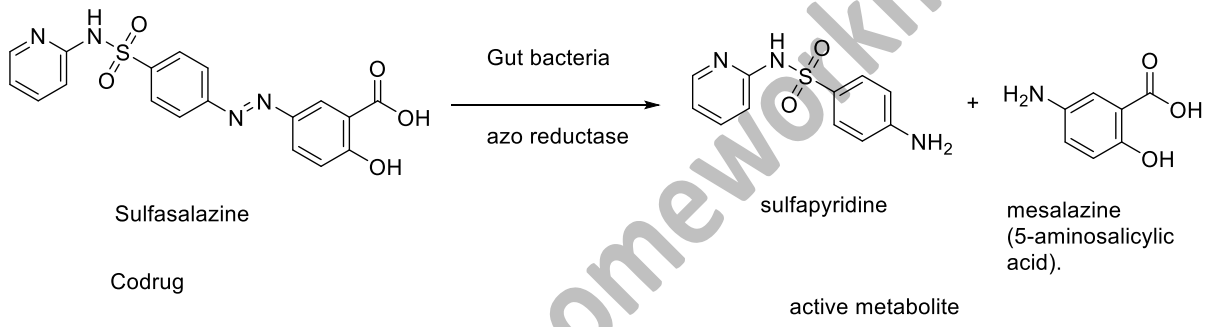



Figure 5: Metabolism of sulfasalazine by gut bacteria.

Parkinson's disease is a neurodegenerative disease and can be treated by L-dopa, which a prodrug. L-dopa is inactive and lipophilic in nature, passing the blood-brain barrier (BBB) to enter the brain. In the brain, L-dopa gets metabolized through aromatic L-amino acid decarboxylase to dopamine. Dopamine is an active drug of L-dopa. But oral administration of L-dopa will be ineffective because it gets metabolized through tyrosine decarboxylase enzyme into dopamine by gut bacteria in the intestine. Dopamine is very polar but unable to cross the BBB (Figure 6) [13].

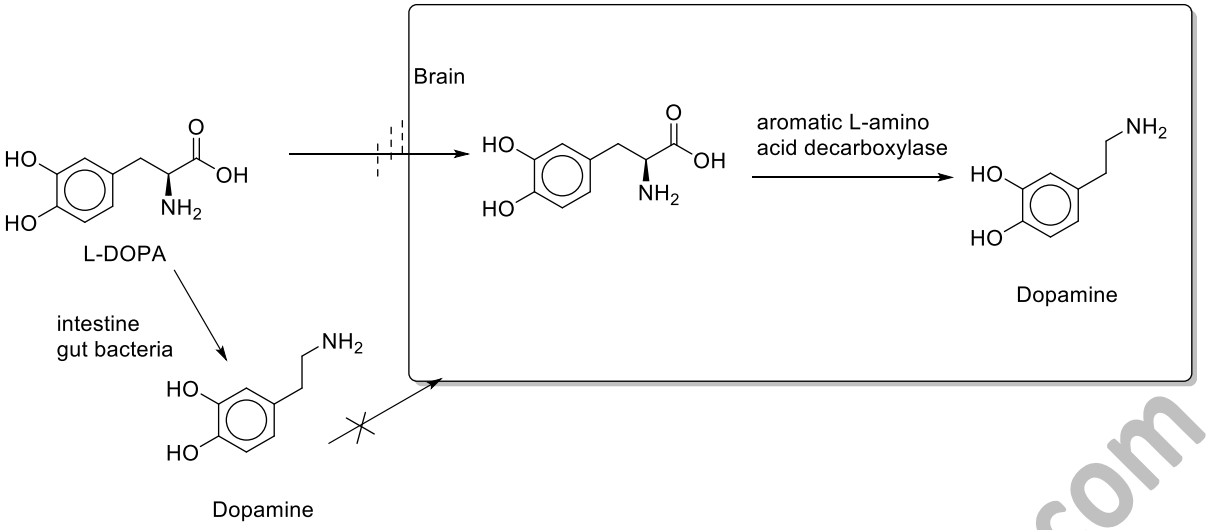



Figure 6: Oral administration of L-DOPA leading to early metabolism.



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