

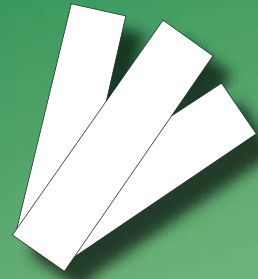
# To the Bitter End: A Case Examining the Genetics of PTC Sensitivity

by

R. Deborah Overath

Department of Life Sciences

Texas A&M University – Corpus Christi



## Part I – Discovery\*

“Arthur,” said C.R. Noller in an irritated voice, “what the heck are you doing over there? Why did you let that awful tasting stuff get into the air? It’s so bitter that I want to vomit!” Drs. Arthur Fox and C.R. Noller were working separately in a lab at the DuPont Chemical Company’s facilities in Wilmington, Delaware.

“What do you mean, C.R.?” snapped Arthur. “I don’t taste anything, and I’m right on top of this stuff.”

“It’s got to be that powder you’ve got there,” retorted C.R. “I’m not working with anything bitter, and I’m too far from the door for it to be coming from outside the lab.”

Arthur was transferring some phenylthiocarbamide (PTC) into a bottle. During the transfer, some of the white powder had dispersed into the air.

“Look,” said Arthur as he licked his finger, picked up a few PTC crystals, and licked his finger again. “I don’t taste anything.”\*\*

“Arthur,” said C.R., “give me some of that stuff. I really don’t want to taste it, but I’ll do it just to prove you’re wrong!”

Arthur Fox brought the bottle of PTC over to C.R. Noller, who picked up a few crystals. As soon as the crystals touched his tongue, C.R. exclaimed, “Yuck! Quick—get me something to rinse out my mouth! That stuff is just too bitter!”

After C.R. rinsed out his mouth with some water, Arthur said, “Let’s see if we can find some other folks to taste this PTC to see if they taste anything.”

For several days Arthur asked all his co-workers, friends, and acquaintances to taste his PTC powder and found that neither he nor C.R. were unique. Regardless of gender, age, or ethnicity, about 60% of people tasted PTC as bitter, like C.R. The other 40% were, like Arthur himself, taste blind: PTC had no taste to them. Arthur also tested closely related chemicals with the same results.

News of Arthur’s discovery was published in *Science*, the premier American science journal (Anonymous 1931). Shortly thereafter Arthur received the following letter:

Dear Dr. Fox,

I read the news of your discovery of variation in the ability to taste phenylthiocarbamide (PTC) and related compounds with great excitement.

I am studying Mendelian markers in human populations. Unfortunately, we have few examples of such traits in humans, as you can see from my

\* The basic facts, scenarios, and players in this case are found in the literature. For example, Arthur Fox did discover variation in PTC sensitivity in the way described, his discovery was a news item in *Science*, and L.H. Snyder did write to Fox as indicated (see Anonymous 1931, Fox 1932, and Snyder 1931a). However, this narrative is a fictionalized account of these events.

\*\* It is important to note that good laboratory practice and safety dictate that chemicals should not be tasted in the laboratory.

article recently published in the Eugenical News (1931b), which I have enclosed. Would you please send me some PTC? I would like to study this variation in tasting ability to see if it is inherited and, therefore, can be used as a Mendelian marker.



Sincerely yours,

L.H. Snyder, Ph.D.  
Professor of Genetics  
Ohio State University

### Questions

1. What does L.H. Snyder mean by the term “Mendelian marker”?
2. What question(s) will Dr. Snyder address in his study?
3. What is his hypothesis?

### References

- Anonymous. 1931. Science news: tasteblindness. *Science* (Suppl.) 73: 14a.
- Fox, A. L. 1932. The relationship between chemical constitution and taste. *Proc. Natl. Acad. Sci. USA* 18: 115–120.
- Snyder, L. H. 1931a. Inherited taste deficiency. *Science* 74: 151–152.
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## Part II – Mendelian Genetics

After obtaining some PTC from Arthur Fox, L.H. Snyder determined the PTC phenotype (can taste or cannot taste) for the members of 100 nuclear families. He first verified that gender was not a factor by comparing the number of male tasters and non-tasters to the number of female tasters and non-tasters. Because there was essentially no difference between sexes, Snyder grouped families by the phenotypes of the parents, disregarding the gender of each parent, and tabulated his data (Snyder, 1931a):

Parent-Phenotype Combinations	No. of families	Phenotypes of Children	
		Can taste	Cannot taste
Both parents can taste	40	90	16
One parent can taste, the other cannot	51	80	37
Neither parent can taste	9	0	17

### Questions

1. What kind of evidence would indicate that the ability to taste PTC is inherited?
2. Why was it important for Snyder to verify that males and females had similar proportions of tasters and non-tasters?
3. Why do couples who can taste PTC have children who cannot?
4. What is the significance of the fact that couples who cannot taste PTC *never* have children who can?
5. Based on these data, what can you conclude about PTC taste blindness? What is your evidence?
6. The second parent-phenotype combination would appear to represent a group of testcrosses. What ratios are expected from testcrosses and what does each ratio represent? These data don't seem to fit either of these expected ratios. How can you explain this?

### Reference

Snyder, L. H. 1931a. Inherited taste deficiency. *Science* 74: 151–152.

## Part III – Molecular Genetics

More than 70 years after Arthur Fox serendipitously discovered that humans vary in their sensitivity to PTC and related chemicals, researchers from the National Institutes of Health, Stanford University, and the University of Utah together discovered the main gene for PTC sensitivity in humans. This gene is a member of a gene family that encodes bitter taste receptors in the mouth called the *TAS2R* gene family (Kim et al., 2003). *TAS2R38*, the gene responsible for PTC taste sensitivity, is on chromosome 7 and codes for a receptor protein responsible for bitter taste perception that binds PTC. The two common alleles differ by three SNPs, causing three amino acid changes. One common allele or haplotype has proline (P), alanine (A), and valine (V) for these three amino acids and therefore is called PAV. The other common allele is called AVI because the amino acids are alanine (A), valine (V), and isoleucine (I). The PAV allele codes for a form of the receptor protein that binds PTC, conferring the ability to taste this chemical. The protein product of the AVI allele cannot bind PTC, and thus this allele confers the inability to taste PTC. However, the fact that the AVI and PAV alleles are expressed equally at the RNA level and that the AVI allele contains no frameshifts or other mutations that would result in early termination of the protein suggests that the AVI-coded receptor protein binds another bitter chemical that has not yet been identified (reviewed in Wooding, 2006). Other haplotypes, presumably due to recombination between the three SNPs, occur but are rare. These rare haplotypes also showed functional responses in *in vivo* studies and, thus, these alleles appear to code for functional proteins (Bufe et al. 2005).

### Questions

1. What is a gene family? What mechanism generates them?
2. What is a SNP? What is a haplotype? How can SNP haplotypes be determined?
3. Assuming the PAV allele is the original one, what types of mutations (silent, missense, nonsense, etc.) have changed the PAV allele into the AVI allele? Explain. Based on the information given, how do these changes fit with what you have learned about the “functional enzyme hypothesis”?
4. You repeat Snyder’s experiment, but instead of determining the ability of each family member to taste PTC, you determine what alleles they carry: 2 PAV (PAV/PAV), 2 AVI (AVI/AVI), or 1 PAV and 1 AVI (PAV/AVI). Using the table provided below, what are the possible outcomes for offspring if the parents have the genotypes described in the first column? Below the genotype, write the phenotype (taster or non-taster) of each kind of individual.

Parent Genotype Combinations	Possible Genotypes/Phenotypes of Children
Both parents PAV/PAV	
Both parents PAV/AVI	
One PAV/PAV, the other PAV/AVI	
One PAV/PAV, the other AVI/AVI	
One PAV/AVI, the other AVI/AVI	
Both parents AVI/AVI	

5. Go back to Snyder's results and give all the possible genotypes for the phenotypes listed in that table.
6. For each step of gene expression, explain how DNA differences lead to phenotypic differences in the ability to taste PTC.
7. Generalizing from this example, what can you say about the connection between Mendelian and molecular genetics? What type of reasoning are you using here?
8. Hypothesize about some consequences of PTC tasting ability in the daily lives of tasters and non-tasters.

### References

- Bufe, B., P. A. S. Breslin, C. Kuhn, D. R. Reed, C. D. Tharp, J. P. Slack, U.-K. Kim, D. Drayna, and W. Meyerhof. 2005. The molecular basis of individual differences in phenylthiocarbamide and propylthiouracil bitterness perception. *Curr. Biol.* 15: 322–327.
- Kim, U.-K., E. Jorgenson, H. Coon, M. Leppart, N. Reisch, and D. Drayna. 2003. Positional cloning of the human quantitative trait locus underlying taste sensitivity to phenylthiocarbamide. *Science* 299: 1221–1225.
- Wooding, S. 2006. Phenylthiocarbamide: A 75-year adventure in genetics and natural selection. *Genetics* 172: 2015–2023.

