

This Week's Citation Classic

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Kellermann G, Shaw C R & Luyten-Kellermann M. Aryl hydrocarbon hydroxylase inducibility and bronchogenic carcinoma. *N. Engl. J. Med.* 289:934-7, 1973.
[Sect. Med. Genetics, Dept. Biology, Univ. Texas, and M.D. Anderson Hosp. and Tumor Inst., Houston, TX]

Aryl hydrocarbon hydroxylase (AHH) is involved in the metabolism of chemical carcinogens and present in many tissues including lung and mitogen stimulated lymphocytes. Its genetic variation in normal subjects can be linked to susceptibility to bronchogenic carcinoma, thus demonstrating a close association between high levels of AHH and this particular cancer. [The SCI® indicates that this paper has been cited in over 345 publications since 1973.]

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"In May 1982, it had been exactly ten years since I walked into Charles Shaw's laboratory at the M.D. Anderson Hospital and Tumor Institute in Houston, Texas, to ask him what kind of project he had in mind for me, having just received a two-year fellowship from the Deutsche Forschungsgemeinschaft. I chose to continue with the aryl hydrocarbon hydroxylase (AHH) project after D. Busbee and E. Cantrell,¹ in his laboratory, had succeeded in demonstrating the presence of the enzyme in mitogen stimulated lymphocytes.

"Using cultured lymphocytes was a very clever idea since it enabled the study of the enzyme, which is not present in the circulating blood, in virtually hundreds and thousands of individuals. All it required was five to ten milliliters of blood. The first population data were encouraging, pointing to a two- to fourfold variation of the enzyme activity in normal subjects. At the same time, I had lined up several volunteers whose 'AHH value' I would check at least twice a week for a period of 18 months. Anyone can imagine this would eventually become a very painful experience but the results were rewarding for all the sufferings. Individual AHH values were highly constant for a given subject indicating some kind of genetic control.

"A large mass of data was necessary to arrive at this conclusion because of the wide variation in

culture and assay conditions. To eliminate some of the variation, my wife, Mieke, had joined me to run all these tests under highly controlled conditions. The most rewarding but also the most exhausting part of the whole research project was the family study designed to support the hypothesis of a genetic control of individual AHH values. My wife and I would drive out to the suburbs of Houston every night to draw blood samples from families, rush back to the lab, and set up cultures. Quite often it was in the early morning hours before we returned home.

"During these long rides there was always one question that kept nagging in my mind: 'What is the relationship, if any, between the enzyme activity of cultured lymphocytes and that of any other tissue such as liver or lung?' I knew the answer to this question was vital and, so to speak, the heart of the entire project. If one were able to establish a firm link between the *in vitro* activity of a certain tissue enzyme, e.g., of the liver, and that of an easily manageable culture system, it would not only allow the carrying out of large population genetic studies on otherwise inaccessible enzymes, but also help one to understand why a genetic variation could be the cause of an increased or decreased risk to contract a particular disease. Therefore, I tried to relate the *in vitro* metabolic rates of some harmless drugs to the lymphocyte AHH activity of the same individual.² The positive results led me to hypothesize that if this relationship between the enzyme activity of cultured lymphocytes and human liver is real, it might not be too farfetched to assume a similar relationship also for the lung. This implied that the genetic variation of AHH activity of lymphocytes reflected genetic variation of lung AHH activity. With this background I did the lung cancer study which in humans linked high AHH activity to an increased risk for lung cancer.

"The reaction and response to this study took me by surprise since I did not immediately realize its full impact in the health field. I never had planned to come up with a new biochemical marker or a test to predict individual cancer risk. To me, it just was an ideal opportunity to study how genetics and environment might interact and whether some common diseases have a genetic basis. Even after nine years the results of the cancer study are still highly controversial mainly because of experimental difficulties. However, growing evidence indicates that the original findings are valid."^{3,4}

1. Busbee D L, Shaw C R & Cantrell E T. Aryl hydrocarbon hydroxylase induction in human leukocytes. *Science* 178:315-16, 1972.
2. Kellermann G, Luyten-Kellermann M, Horning M G & Stafford M. Elimination of antipyrine and benzo(a)pyrene metabolism in cultured human lymphocytes. *Clin. Pharmacol. Ther.* 20:72-80, 1976.
3. Nebert D W. The Ah locus, a gene with possible importance in cancer predictability. *Arch. Toxicol. Suppl.* 3:195-207, 1980.
4. Rüdiger H W, Hehlig V & Hahn E. Enhanced benzo(a)pyrene metabolism and formation of DNA adducts in monocytes of patients with lung cancer. *J. Cancer Res. Clin. Oncol.* 96:295-302, 1980.