J. Soc. Cosmetic Chemists, **21,** 99-106 (Feb. 4, 1970)

Primary Odor Correlated with Molecular Shape by Scanning Computer

JOHN E. AMOORE, Ph.D.*

Presented May 8, 1969, New York City

Synopsis—The human sense of smell is probably based on distinct primary ODORS. An experimental method is described for identifying and mapping out the chemical extent of one of the primary odors, represented by the sweaty odor of ISOVALERIC ACID and its homologs and isomers (to which certain persons are specifically "odor-blind"). The production of this primary odor is shown to require the carboxylic acid functional group, in conjunction with a limited range of MOLECULAR SHAPES and sizes.

Silhouette photographs of scale molecular models are rapidly scanned and compared by a television camera linked to a COMPUTER. A correlation coefficient as high as 0.8 has been obtained between molecular shape and odor quality.

A survey is being planned with the objective of identifying all the primary odors, which may eventually reach 20 to 30 in number. Some implications of this "olfactory code" for cosmetic chemistry are briefly discussed.

INTRODUCTION

In 1962, two papers describing the stereochemical theory of olfaction were published (1, 2). At that time just seven primary odors were described. Several years have since passed and it seems appropriate now to review progress in this subject.

In short, there have been three main advances. The first rigorous experimental method has been developed for identifying a human primary odor (3–5). A computer procedure has been adapted for relating odor quality to molecular shape (6). Furthermore, it has proved necessary to raise the limit on the probable number of primary odors, from seven to perhaps nearer 27 (7).

* Western Regional Research Laboratory, Agricultural Research Service, U. S. Department of Agriculture, Albany, Calif. 94710.

These three principal trajectories are described in the cited references. In the present article the main results are sketched, and some opinions are offered on how these findings may eventually influence cosmetic chemistry.

IDENTIFICATION OF THE "SWEATY" PRIMARY ODOR

The French physicist Marcel Guillot has many acquaintances in the perfumery industry. He himself is totally unable to smell the macrocyclic musks, although his sense of smell appears otherwise satisfactory. On inquiry, he found that many creative perfumers and essential oil chemists are aware of some personal "blind spot" as regards a particular odor. He mentioned macrocyclic musks, steroid musks, benzyl salicylate, methyl ionone, and farnesol, plus a few others (8). With remarkable insight, he suggested that these "anosmies partielles" may correspond with a deficiency for the affected person in the nerves signalling the corresponding "odeurs fondamentales." Hence, the systematic study of odor-blindness, or "specific anosmia," should lead to an enumeration of the "primary odors" of the human sense of smell.

Although Guillot's suggestion was made 20 years ago, there seems to have been no attempt to exploit it until very recently (3). The research work in this laboratory required close attention to detail, but was not inherently difficult (4). A newly-reported example of odor-blindness, that to the sweaty odor of isobutyric acid, was studied. About 2% of the people are unable to smell this compound until the concentration is elevated approximately 50 times compared with the normal detection threshold for the average observer. The defect is specific, because these same people have no problem detecting other, unrelated odors.

Here a word of warning should be interpolated. It is necessary to take quite extraordinary precautions as regards the olfactory purity of the isobutyric acid sample. Any trace of impurity can be smelled by the anosmic observers, even though it may not show up on the gas chromatograph. This point is liable to be imperfectly appreciated by critical reviewers or intending experimenters in the field of chemical constitution/odor quality relationships. An expert perfumer of the author's acquaintance was frequently surprised at the changes in the odors of many supposedly familiar lower fatty acids following meticulous purification.

The results for isobutyric acid are illustrated in Fig. 1. A group of 86 normal observers had personal detection thresholds distributed in a roughly bell-shaped curve. Meanwhile, the panel of 10 specific anosmics (found by screening an entire staff of 400-plus) exhibited thresholds more

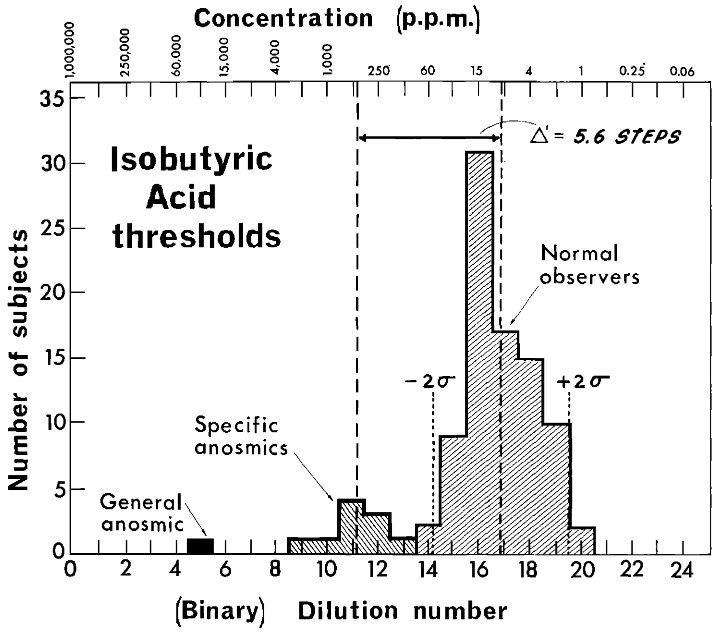

Figure 1. Isobutyric acid thresholds. (Reproduced from ref. 5 by courtesy of N. Tanyolac)

than twice as high as the standard deviation limit. The key measurement is the difference (Δ) in sensitivity between the normal and specifically anosmic subjects. The average defect toward isobutyric acid was 5.6 binary steps, where each step represents a doubling of the odorant dilution (in water).

Similar graphs were prepared for various chemical relatives of isobutyric acid, each time measuring the olfactory defect (Δ) of the specific anosmics. The same panel of 10 specific anosmics was used throughout. The consolidated results are shown in Fig. 2. First of all, it is apparent that only the fatty acids exhibit any notable defect. The corresponding aldehyde, alcohol, or ester was smelled without difficulty; this is hardly surprising, as they have quite unrelated odors. Hence, the necessary functional group for this primary odor is exclusively specified as the carboxylic acid grouping —COOH. Next, the first 10 normal (straight-chain) fatty acids may be considered. The deficiency of the anosmic subjects was at a maximum from four to seven carbon atoms in the chain. This result establishes the preferred molecular size for a fatty acid to develop this primary odor. Finally, the effect of changing molecular shape was examined by testing several structural isomers (branched-chain) in the favorable molecular size range. The greatest defect for the specific

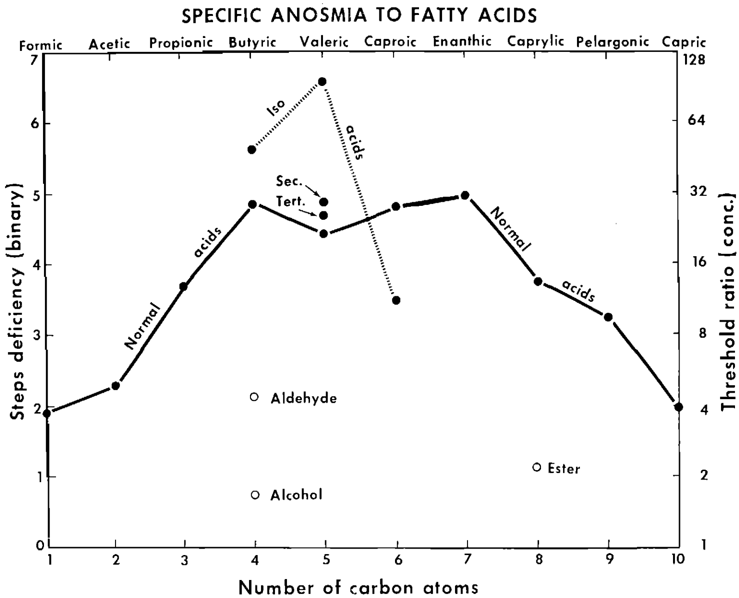

Figure 2. Specific anosmia to fatty acids. (Reproduced from ref. 5 by courtesy of N. Tanyolac)

anosmics was encountered with isovaleric acid, which therefore has the most appropriate molecular shape for producing this odor (3).

There are many other isomers that could be tested, but for the time being it may be concluded that isovaleric acid must be very close to being the ideal stimulant for producing this primary odor. It also has the lowest detection threshold (for normal observers) among all the fatty acids tested. The smell of purified isovaleric acid is a plain monolithic sweat-like odor, with little if any trace of other nuances. Hence, it was determined that isovaleric acid has virtually a true primary odor (sweaty). It represents the first human primary odor to be established by an objective systematic experiment method.

Molecular Shape Scanned by Computer

No microscope can yet reveal to our eyes a molecule the size of a typical odorant. Nevertheless, enough has been learned about molecular structure to permit us to build accurate scale models. These models form the basis for deductions about the relationships between molecular shape and odor. The conformation and orientation of the molecular model is established to a fixed set of rules based on physical chemistry.

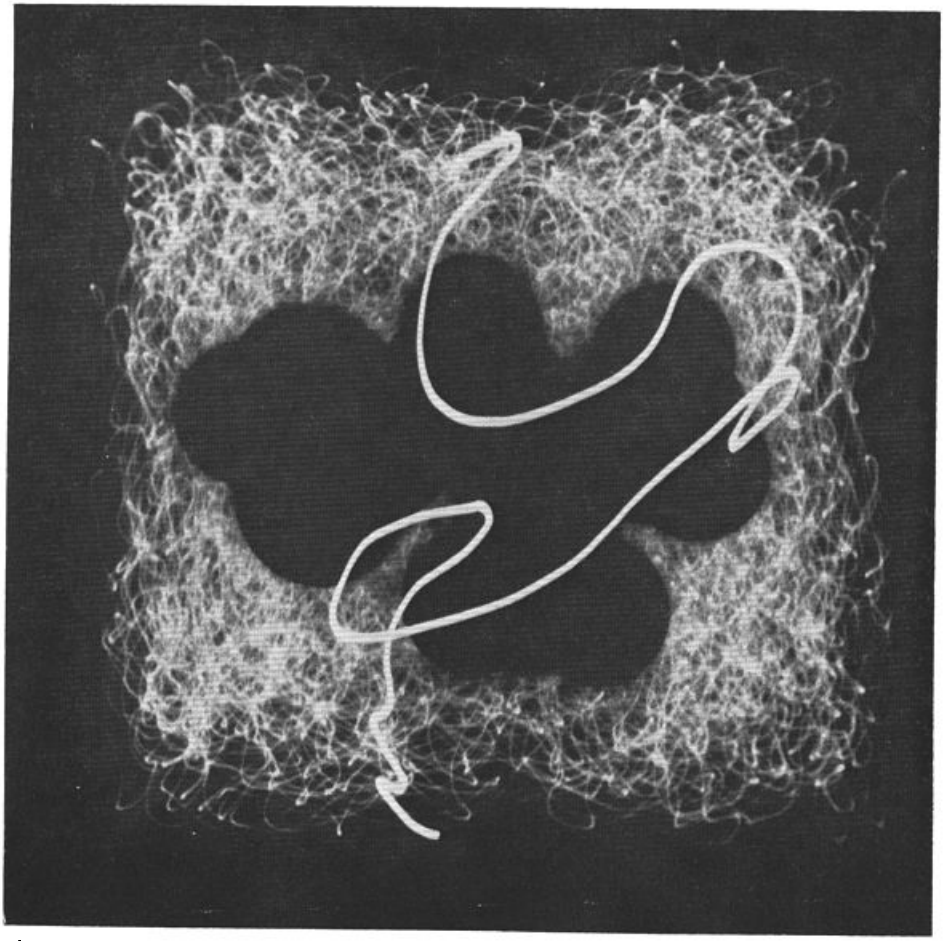

Figure 3. Black silhouette from molecular model of isovaleric acid. (Photo courtesy of G. Palmieri and E. Wanke, University of Genoa)

The model is photographed in silhouette from three directions mutually at right angles.

The silhouette photographs are then sent to Prof. G. Palmieri at the University of Genoa, Italy. He has developed a unique pattern-recognition machine, known familiarly as "PAPA." This consists of a modified television camera linked directly to a special computer (9). The machine scans the molecular silhouette by means of a large, reproducible collection of random lines (Fig. 3). The instrument is first "trained" on the silhouette photograph of the isovaleric acid molecule, which was

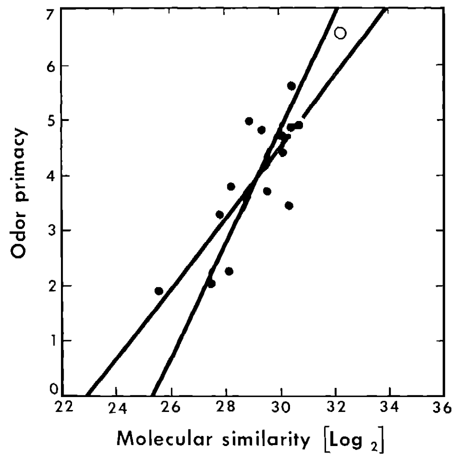

Figure 4. Correlation of primary odor with molecular shape for 15 fatty acids. Threshold difference for each acid is correlated with the degree to which its molecular shape resembles that of isovaleric acid itself (open circle). Both regression lines are shown because both variables are subject to experimental error. (Reproduced from ref. 6 by courtesy of the Editor of *Nature*)

selected as the standard compound for the sweaty primary odor. When the machine is subsequently shown photographs of other molecular models, it compares their sizes and shapes by computing the frequencies with which each random line intersects each silhouette. The degree of molecular similarity, assessed by 4,096 random lines, is printed out within five seconds.

The final crucial test can now be performed. Do the measurements of primary odor quality correlate with the measurements of molecular shape? Indeed they do (6). The results for 15 fatty acids are given in Fig. 4. The molecular similarity values were those obtained from the PAPA machine. The "odor primacy" measurements are the olfactory deficiencies experienced by the specific anosmics, expressed in binary steps. The trend of the correlation is very apparent. The correlation coefficient for this graph is 0.80 (maximum for a straight line would be 1.0). This is a very encouraging result, considering the sources of error and approximation (human variability, problem of chemical purification, simplified molecular modeling). It shows without doubt that there is a strong correlation between molecular shape and odor quality. If it were known that a compound is a fatty acid, it should be possible to make a fair prediction, from its molecular shape, of how much primary sweaty odor character it ought to possess.

How Many Primary Odors Are There?

This question is often asked, but no definite answer is possible at present. However, the first steps are being taken towards a solution. All available information on different chemical examples of specific anosmia (7) has been collected and the total presently stands at 62. There is, nevertheless, a good deal of redundancy among these observations, with certain compounds clearly belonging to the same primary odor. For example, several fatty acids have been noted, but they presumably belong to the same sweaty primary odor. A number of macrocyclic musks exhibit anosmias, but they most likely belong to a single musk primary or to one of the possible subdivisions of the musk class.

A tentative estimate at the moment would be that the total number of primaries will come out between 20 and 30, with 27 as a likely figure. At present, a major investigation on all the primary odors is being planned. As each primary will require at least one man-year of professional-level work, this is a formidable undertaking. It would be a considerable help to the author to hear about any examples of specific anosmia, as this may fill a gap in the odor spectrum to be covered (10).

The total problem of the primary odors may be regarded as the problem of the "olfactory code." At the moment, we have learned only one word of this code, the "sweaty" primary odor of isovaleric acid. However, the first step is often the hardest. In the author's opinion, this first primary odor has as much significance for odor science, as that first codon (UUU for phenylalanine) of the well-known genetic code had for molecular biology. Let us hope that equally vigorous research will develop in many laboratories as an attack on our olfactory code.

Likely Significance for Cosmetic Chemistry

In several more years the "olfactory code" will very likely be solved, and possibly even be confirmed by independent methods. The scientific challenge is there, and the experimental methods are available. The odor chemist would then be in possession of theoretical guidelines equivalent to the color chemist. The great industries of color printing, color photography, and color television all depend on the centuries-old concept that any color can be reproduced by appropriate mixture of three primaries (red, green, and blue lights).

It would be wise to anticipate what effect this could have on the aroma/flavor industry. At its simplest, it would mean that any intended fragrance could be matched by an appropriate mixture of a standard set of (say) 27 aromatics. This facility might have a use in high-volume formulations, such as could be needed for marine and petroleum-grown food products for mass feeding to avert starvation.

Quality preparations will continue to need the skills of the expert creative perfumer, because there are supplementary problems of component fixation, constancy throughout evaporation, and interactions between compounds, that are not touched upon by a blind admixture of primary odor ingredients. However, knowledge of the physiological primary odors could be expected to help in several ways. It would allow assignment of the chemical species in a complex perfume to their constituent primaries, and this might lead to a simpler formulation which could achieve the same olfactory effect with fewer components. Stereochemical assessments of molecular models could suggest single chemical compounds that might unite in one molecule the desirable aroma attributes that must presently be contributed by a mixture. Perhaps selective instrumental sensors could be designed that would assay the intensity of each primary odor in a mixture, hence forming the basis for computerized monitoring and control of perfume or flavor formulation.

At the moment, these are merely ideas; but it is believed that the solution to the olfactory code, when it occurs, will prove to be as significant for cosmetic chemistry as the advent of the gas chromatograph.

(Received May 21, 1969)

References

(1) Amoore, J. E., The stereochemical theory of olfaction, 1, identification of the seven primary odors, *Proc. Sci. Sect. Toilet Goods Assoc.*, **37,** Spec. Suppl., 1–12 (October, 1962).

(2) Amoore, J. E., The stereochemical theory of olfaction, 2, elucidation of the stereochemical properties of the olfactory receptor sites, *Ibid.*, 13–23 (October, 1962).

(3) Amoore, J. E., Specific anosmia: a clue to the olfactory code, *Nature,* **214,** 1095–8 (1967).

(4) Amoore, J. E., Venstrom, D., and Davis, A. R., Measurement of specific anosmia, *Percept. Mot. Skills,* **26,** 143–64 (1968).

(5) Amoore, J. E., *Specific Anosmias and Primary Odors,* in Tanyolac, N., *Theories of Odor and Odor Measurement,* Robert College, Istanbul, Turkey, 1968, pp. 71–85.

(6) Amoore, J. E., Palmieri, G., and Wanke, E., Molecular shape and odour: pattern analysis by PAPA, *Nature,* **216,** 1084–7 (1967).

(7) Amoore, J. E., *A Plan to Identify Most of the Primary Odors,* in Pfaffmann, C., *Olfaction and Taste III,* Rockefeller University Press, New York, N. Y. (in press).

(8) Guillot, M., Anosmies partielles et odeurs fondamentales, *Compt. Rend.,* **266,** 1307–9 (1948).

(9) Palmieri, G., and Wanke, E., A pattern recognition machine, *Kybernetik,* **4,** No. 3, 69–80 (1968).

(10) Amoore, J. E., Are you "odor-blind?", *Drug Cosmetic Ind.,* **102,** 128 (February, 1968).