TECHNICAL PAPERS

Synthetic Caffeine

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The identity of a synthetic compound with a natural product is usually made by the determination of physical constants such as the melting point, mixed melting point, and elementary analysis. However, with the many pharmacologically active substances, such as hormones and vitamins, a biological assay has been employed to supplement chemical identification. This appears important and necessary, because sometimes the physical constants do not completely establish the absolute purity of the product. Recently, for example, there was encountered in this laboratory a sample of synthetic pyridoxine which answered the specifications of *New and nonofficial remedies* (*4*), but which proved to be much more toxic than the standard.

Synthesis of caffeine and theobromine was initiated by Fischer and his co-workers (*1*), and newer methods of synthesis, partial or complete, have been achieved by other investigators (*5*). Previously, we studied the synthetic alkyl derivatives of theobromine (*3*). As an extension of the above work, it occurred to us that pharmacological proof of identity of totally synthetic caffeine and commercial caffeine made from a natural intermediate was desirable. The latter is usually prepared by methylation of theobromine. Samples of both were generously supplied by L. P. Kyrides, research director of the Monsanto Chemical Company, St. Louis, Missouri. The melting point of commercial caffeine ranged between 234.5 and 237° C.; that of synthetic caffeine, between 234.5 and 237.5° C.; and the mixed melting point, between 235 and 237° C.

Two types of experiments were carried out—one, the measurement of the stimulation of the central nervous system in rats; the other, the comparison of toxicity in mice by intravenous injection. The central stimulating action was evaluated in spring-suspended cages according to the method of Schulte and co-workers (*2*). Ten rats, weighing between 230 and 280 grams, were employed. A fixed dose of 20 mg./kg. of each drug in 0.5 per cent solution was injected subcutaneously. The observation period was exactly 4 hours, counting from the time of injection. Five animals received synthetic caffeine, and the other 5, the commercial. On the following day a cross-over test was made—those receiving the synthetic caffeine the previous day received the commercial, and vice versa.

For the toxicity study, mice weighing from 14.6 to 19.3 grams were used. The concentration of the solution was the same as for rats (0.5 per cent). Both samples were run on the same day.

The results are unequivocal. The average number of revolutions recorded from the cages by the 10 rats for commercial caffeine was 34.8; for synthetic caffeine, 34.1; and that of the control test (without medication), 5.1. The median lethal dose (LD_{50}) by intravenous injection of commercial caffeine in 30 mice was found to be 79.36 ± 6.94 mg./kg. The LD_{50} of synthetic caffeine in 30 other mice was determined to be 75.51 ± 5.39 mg./kg. There is no significant difference between the two figures statistically.

Pharmacological results indicate, therefore, that commercial caffeine and synthetic caffeine have the same degree of central stimulation and toxicity.

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Visibility of the Deer Fly in Flight[1]

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Visual acuity while viewing a moving object is a matter which has received little attention. In fact, the only reference bearing remotely on this subject which I have been able to find is a note by Irving Langmuir (*1*). Dr. Langmuir has ingeniously demonstrated that the speed of 818 miles/hour attributed to the deer botfly by the *Illustrated London News* (*4*) is excessive. As Dr. Langmuir expresses the matter, the insect must consume "1.5 times his own weight of food each second" in order to maintain this velocity.

To establish the approximate speed of the fly, Dr. Langmuir conducted an experiment which he describes as follows:

"...I took a short piece of solder about 1 cm. long and 0.5 cm. diameter and tied it about its middle to one end of a light silk thread, holding the other end in my hand. With lengths of thread of from 1 to 3 feet it was easily possible to swing the weight in a circle in a vertical plane at the rate of 3 to 5 rotations per second (timed with a telechron clock).

[1] This investigation was supported in part by a grant from the American Optical Company.

In this way speeds from 13 to 64 miles per hour were produced.

"Observations in a room, with a brightly lighted white ceiling as background, showed that at 13 miles per hour (580 cm./sec.) the 'fly' was merely a blur—the shape could not be seen, but it could be recognized as a small object of about the correct size.

"At 26 m./hr. (1,150 cm./sec.) the fly was barely visible as a moving object. . . ."

He concludes that "a speed of 25 miles per hour is a reasonable one for the deer fly."

It may well be that energy considerations limit the speed of the deer fly to a mere 25 miles/hour, but I wish to give evidence indicating that the fly would be visible at much higher linear velocities. Neither the article in the *Illustrated London News* nor the original article by Dr. Townsend (*2*) states at what distance the fly was observed. Had Dr. Langmuir been able to produce similar rotations with a thread 94 instead of 3 feet long, it seems likely that his artificial "fly" would have been visible though traveling at over 100 miles/hour. The reason is that the acuteness of human vision is diminished not by the linear, but by the angular, velocity of the object viewed.

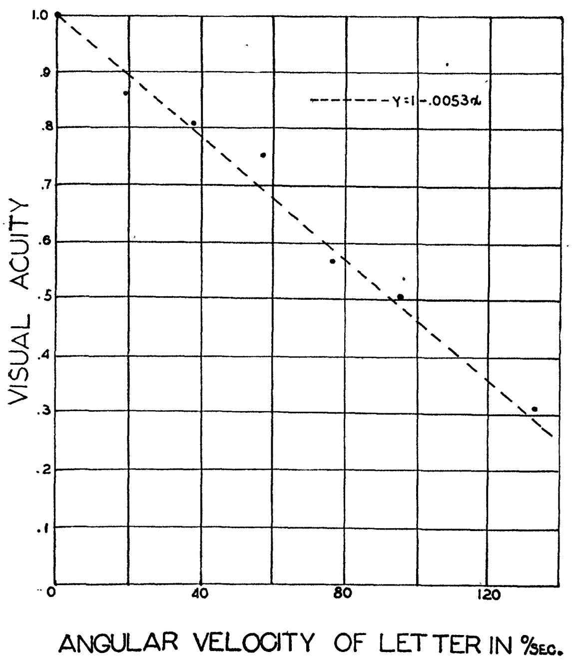

FIG. 1

The data presented in Fig. 1 show some results I obtained during a general experimental investigation of visual acuity while viewing a moving object. The data are for constant angular velocity in the horizontal plane. The test objects were Snellen letters.

The expression $y = 1 - .0053x$ is a fair empirical fit to the data. A stationary black disc on a white background can be seen when it subtends an angle of 25–30″ of arc at the eye, and the corresponding value for a stationary black line on a white background is 4–6″ of arc (*3*). The artificial fly presents a roughly rectangular cross section to the eye, and we may assume an intermediate value of 18″, or .005°, as the angle necessary for vision when the fly is stationary. The angle necessary for vision when acuity is reduced by moving the fly is, then, $\beta = \dfrac{.005°}{1-.0053\,\alpha}$, where α is the angular velocity in degrees per second. This velocity equals approximately $57.3\,\dfrac{v}{r}$, where v is the linear velocity in feet per second and r the distance to the object in feet. The angle, θ, subtended by the fly, is approximately $57.3\,\dfrac{s}{r}$ in degrees, s being the size of the object in feet.

For visibility, $\theta = \beta$, or $57.3\,\dfrac{s}{r} = \dfrac{.005°}{1 - .304\,\dfrac{v}{r}}$. From this,

$$v = 3.29\left(r - \frac{.005\,r^2}{57.3\,s}\right) \text{ and } \frac{\partial v}{\partial r} = 3.29\left(1 - \frac{.01\,r}{57.3\,s}\right).$$

It appears that the highest velocity with good visibility will occur when $r = 5{,}730\,s$. Taking Dr. Langmuir's value of .5 cm., or .0164 feet, for s, we find that the optimum distance for observation of the fly is 94 feet. At a distance of 3 feet, the fly would begin to blur at about 7 miles/hour, a figure in substantial agreement with Dr. Langmuir's observations. However, at a distance of 94 feet and with contrast and other conditions of vision optimal, the deer fly might be seen while traveling at 105 miles/hour, if it can fly that fast.

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Production of Yellow Bean Mosaic in Beans by Virus From Mottled Gladiolus

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The first observation conducive to this record of an improbable source of Bean Virus 2 was made by Carl Robertson, of the Eugene Fruit Growers Association, Eugene, Oregon. In 1939 Mr. Robertson asked local pathologists interested in vegetable diseases to observe a field of *Phaseolus vulgaris* L. var. Blue Lake, planted contiguous to a field of *Gladiolus* spp. He wished confirmation of his observation that a gradient infection of mosaic extended from the row nearest the gladioli to a distance of approximately 150 feet, and of his opinion that the gladioli were the probable source of the virus. While the correlation between high mosaic percentage in the bean planting and the nearness of gladiolus plants was amazing, we supposed the apparent correlation was nonsignificant, having found an occasional mosaic-diseased clover plant in

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