The italicized part is a typical cycle and it repeats indefinitely.

This method is quite general and is applicable to other systems as well as to the diadic system. If $p=3$ (triadic system), $B=14=3^0 \cdot 14$ with $k=0$, $m=14$. The exponent of 3 modulo 14 is 6 ($s=6$), and $3^6-1=52 \cdot 14$, $C=52$.

$$\left(\frac{5}{14}\right)_{10}=\frac{5 \cdot 52}{3^6}\left(\frac{1}{1-3^{-6}}\right)=$$

$$\frac{100122}{1000000}(1+0.000001+$$

$$0.000000000001+\ldots)_3=$$

$$(0.100122\mathit{100122}100122\ldots)_3$$

The expression for $(5/14)_{10}$ as a fractional in the triadic system also repeats indefinitely with the italicized part as its period.

If the numerator 5 is divided directly by the denominator 14 in the decadic system, one has

$$\left(\frac{5}{14}\right)_{10}=(0.357142\mathit{857142}8571428\ldots)_{10}$$

This is also a periodic affair with the italicized part as its period; it could have been obtained in the same manner as for the diadic and triadic systems illustrated previously. The process of encoding rational fractions into fractionals in the general p-adic system is somewhat more laborious than that of encoding an integer, but it is not necessary that the rational fractions be converted into decimals in the decadic system first.

DAVID K. CHENG
Electrical Engineering Department
Syracuse University, Syracuse, New York

Reference

1. See, for instance, J. V. Uspensky and M. A. Heaslet, *Elementary Number Theory* (McGraw-Hill, New York, 1939), Chap. 8.

21 March 1956

Some Serotoninlike Activities of Lysergic Acid Diethylamide

In 1954 Woolley and Shaw (*1*) proposed that serotonin was of importance in the maintenance of normal mental functions. The reason for this idea was that a variety of chemical compounds (ergot alkaloids, harmala alkaloids, yohimbine, certain synthetic analogs of serotonin, and so on) had been found to cause mental disturbance in animals (including man) and could be shown to act as antimetabolites of serotonin when they were tested on smooth muscles. Thus various ergot alkaloids had been shown to act as antimetabolites of serotonin on sections of carotid arteries (*2*) and on isolated rat uteri (*3*). The most active of the ergot derivatives when tested on these isolated tissues was lysergic acid diethylamide (LSD-25).

Because LSD-25 was also remarkable for its high activity in causing hallucinations in human beings (*4*), the aforementioned hypothesis seemed reasonable. The LSD-25 and other hallucinogens, which were demonstrably antimetabolites of serotonin, were pictured as causing their effects on mental processes by bringing about a deficiency of serotonin in parts of the brain. Such pharmacologically produced deficiency of serotonin was evidently the cause of the action of these drugs on the smooth-muscle preparations, and the same explanation might be applied to nerve tissue. Indeed, some of the synthetic antimetabolites of serotonin were shown to act on glial cells of the brain cultured *in vitro* much as they did on smooth-muscle preparations (*5*). However, this idea of the mental effects arising from a deficiency of serotonin in the brain is a working hypothesis. The notion that the drugs bring about a cerebral excess of the hormone, rather than a deficiency, also must be considered (*6*).

We wish now to report some testing procedures in which LSD-25 acted like serotonin rather than as an antagonist. These procedures employed the isolated heart of the clam (*Venus mercenaria*) and the anesthetized dog. Welsh has shown that serotonin stimulates the heart of *V. mercenaria* and causes an increase in the amplitude of the beat. He also reported that this action of the hormone was antagonized by LSD-25 (*7*). We have attempted to repeat this latter observation but have found that, instead of acting as an antiserotonin, LSD-25 (*8*) acted like serotonin. Similar observations have been communicated to us by H. Hoagland. Discussion of our results with Welsh has shown that he now finds the same phenomenon with *V. mercenaria* obtained in America. His earlier findings had been with a European variety. Here, then, is an isolated organ for which LSD-25 acted like serotonin and in which it was more potent, weight for weight, than the hormone itself.

A second situation in which LSD-25 acted like serotonin was in raising the blood pressures of anesthetized dogs. In such animals the intravenous injection of serotonin causes a transient rise in pressure. It is well known that, depending on the dose, the rate of injection, and the individual character of the animal, one may see other responses, such as a fall in arterial pressure preceding the rise, or one may see a sharp rise superimposed on the initial fall, followed by a secondary rise (*6, 9, 10*). This same variability has now been seen in responses to LSD-25. Both pressor and depressor phases could be observed (Fig. 1). Six dogs were anesthetized with Nembutal and calibrated with serotonin as previously described (*10*). They were then tested with graded doses of LSD-25, in-

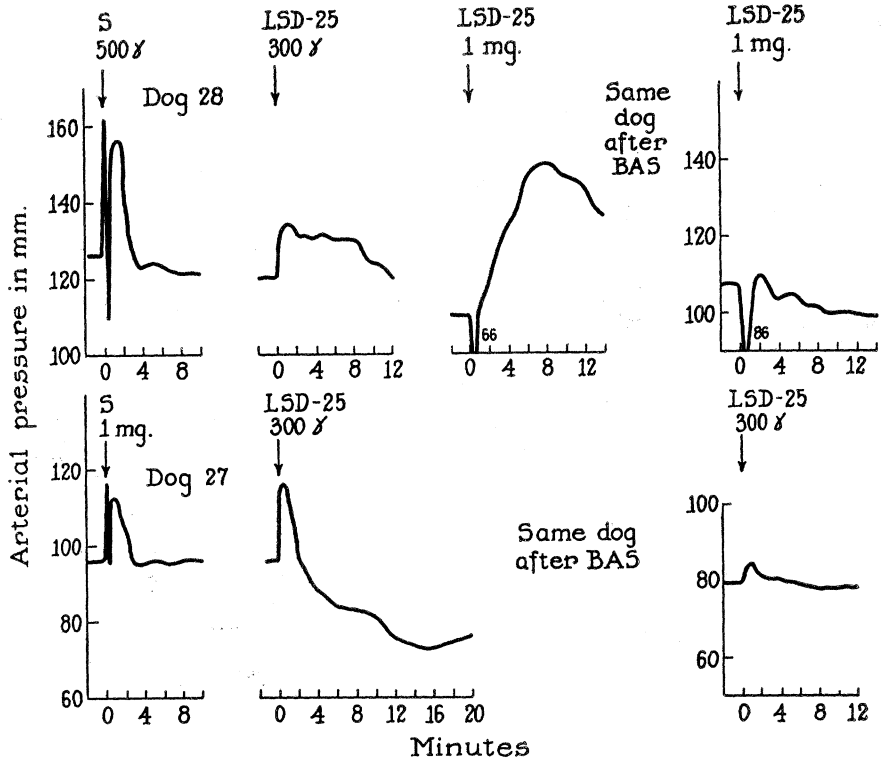

Fig. 1. Arterial pressure responses of dogs intravenously given serotonin (S) and LSD-25 before and after the antimetabolite of serotonin (BAS). Fifty milligrams of BAS was injected intravenously 1 hour before the last dose of LSD-25. Numbers under the profound pressure drops indicate the lowest pressure obtained.

jected into the jugular vein. Quantitative comparison of rises induced by serotonin and by LSD-25 as a pressor agent showed that the LSD-25 was 1 to 3 times as active as serotonin (on a weight basis).

The pressor action of LSD-25 could be prevented by prior treatment of the dog with the new and powerful antimetabolite of serotonin—namely, 1-benzyl-2,5-dimethylserotonin, or BAS (*10, 11*). BAS has been shown to be quite specific, in that dogs protected against serotonin with it are not protected against the pressor effects of adrenaline. The curves will show that BAS protected the dogs against the pressor effects of LSD-25 (*12*).

A third type of experiment in which LSD-25 showed an action similar to that of serotonin has been described by Marrazzi and Hart (*13*). This was the inhibition of synaptic transmission in the optic cortex of the cat. It is therefore clear that one can find both serotoninlike and antiserotonin actions of LSD-25. In fact, both types of effect may be seen in one preparation. Thus, dogs given LSD-25, as in the afore-described experiment, were found to be partially protected against the pressor action of serotonin when it was subsequently injected. In thinking about these facts one should not forget that dogs, as well as isolated organs, can be protected against the effects of serotonin by serotonin itself (*10, 14*).

Although this possession of both serotoninlike and antiserotonin action may seem perplexing in the extreme, it need not be so. One may picture serotonin as acting on tissues by combination with a receptor specifically designed to react with it. One may also picture these receptors as not all of one kind but varying slightly from tissue to tissue (*15–17*). Serotonin combines with these receptors and, in so doing, causes a contraction of the tissue, just as acetylcholine is believed to do when it combines with its specific receptors (*18*). An antimetabolite such as BAS combines with the serotonin receptors in such a way that serotonin cannot reach them, but still, because the "fit" is not perfect, the BAS does not cause the contraction. It thus blocks the action of serotonin but at the same time does not fulfill the function of the hormone. LSD-25 also because of its structural analogy to the hormone combines with these receptors. From some kinds—for example, those in isolated segments of carotid arteries or in rat uterus—it acts like BAS and blocks the action of serotonin without at the same time causing a serotoninlike contraction. For other kinds of serotonin receptors—for example, those in *V. mercenaria* hearts—the LSD-25 not only combines with the receptors but is able to induce a serotoninlike effect, presumably because the "fit" is good enough. The antiserotonin action of serotonin itself then may be pictured merely as the combination of two or more molecules of serotonin with one receptor site. This site is then blocked because it has not combined with a single molecule of serotonin but rather with several. As was pointed out earlier (*10*), this is the classical picture of inhibition of an enzyme by an excess of its substrate and seems applicable here as well.

Do these findings of a serotoninlike action of LSD-25 mean that we can decide between the alternate explanations of an excess and a deficiency of serotonin in the causation of mental disease as pictured in references 1 and 6? It seems unwarranted to answer this question now. In the first place, the concept does not depend on the hallucinogenic effects of LSD-25 alone but rather on the central actions of a variety of analogs of serotonin—namely, harmine, yohimbine, medmain, and so on. It will be necessary to demonstrate that all of these analogs have serotoninlike activities if the theory of excess is to prevail (*19*). Furthermore, the abnormal (psychotic?) behavior induced in mice by LSD-25 has been prevented by serotonin (*20*). This might argue in favor of the hallucinations being manifestations of deficiency. Nevertheless the antiserotonin action of excess serotonin itself may obscure this conclusion. It would seem that both possibilities (excess and deficiency) must be kept in mind until a more crucial means of testing becomes available.

E. SHAW
D. W. WOOLLEY*
Rockefeller Institute for Medical Research, New York, New York

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Gamma-ray Activity of Contemporary Man

Measurements of the natural gamma-ray radioactivity of the human body have been reported recently by several workers who made use of large ionization chambers (*1*) or liquid scintillation counters (*2*) surrounding the subject to be investigated. These apparatus, however, do not have adequate spectrometric properties to permit identification of the radioelements involved.

In our laboratory, following successful reduction of the background radiation by shielding and choice of crystal canning material (*3, 4*), we have availed ourselves of a NaI scintillation crystal (10.8 cm in diameter and 3.8 cm thick) mounted on a DuMont 6364 phototube connected to a Marconi 24-channel pulse analyzer (5). Whole body radiation was measured by placing the face of this crystal 8 cm from the back of a seated person at the height of the twelfth thoracic vertebra (*6*). Background readings were obtained with a similarly placed mockup consisting of distilled water in steel cans. As a standard of K^{40} activity, 2 lb of KOH (C.P.) in sealed bottles was used at a distance of 40 cm. Geometric and scattering parameters *in vivo* were determined experimentally by the use of a few microcuries of K^{42}, the gamma ray of which has sensibly the same energy as that of K^{40}. The short-lived isotope solution was divided into two equal parts, one of which was administered to the subject and the other of which was retained as an intermediate radioactive standard after dilution in a mass of water of electron content equivalent to the 2 lb of KOH. Comparisons were made *in vivo* 10 hours or more after ingestion in order to attain equilibrium between K^{42} and K^{40}.

Preliminary pulse-height spectra of the radiation emitted by uncontaminated members of our staff were obtained in early 1955 (*7*). They disclosed potassium as essentially the only radioelement, in amounts corresponding to 0.22 percent of body weight in men and 0.16 percent in women. Inasmuch as this activity represents about 10^{-8} c of gamma radiation,