

5-HYDROXYTRYPTAMINE AND BUFO—AN ATTEMPT AT SYNTHESIS

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"ALTHOUGH it is as long ago as 1933 since a basic substance, active in stimulating movements of the intestinal tract, was detected in extracts of intestinal mucosa in the laboratory of Dr. Erspamer, it was nearly twenty years before this "enteramine" was identified as 5-hydroxytryptamine; in the meantime the latter had been shown by Dr. Page and his co-workers to represent the constitution of the serotonin which they had isolated from blood serum."¹

5-HT is widely distributed in nature and has been found in mammals, birds, reptiles, amphibia, fish, molluscs, arthropods, sea anemones, and also in stinging nettles. As regards mammals, birds, and reptiles, its chief site appears to be the gut. In cephalopods (*Octopus vulgaris*), it is found in the posterior cervical glands, in gastropods (*Murex trunculus*) in the hypobranchial body; and it is the venom of the wasp and spider, and the sting fluid of the stinging nettle which contain this interesting substance. In the last mentioned groups it is connected with survival, means of killing prey, feeding, and defence. The victim may succumb, or suffer only local ill-effects. In how far is 5-HT responsible for the toxic effects of venoms and sting fluid? Is the presence of 5-HT in these several phyla—Vertebrata, Tunicata, Mollusca, Arthropoda, Angiospermae—a coincidence? Or has it a functional or evolutionary significance? Will even a superficial study of its occurrence and possible action give some idea as to the mode of action of remedies which contain it?

In man, though widespread, its distribution is limited to certain tissues and types of cells. It seems as if the enterochromaffin and argentaffin cells are responsible for its secretion and those are to be found chiefly in the gastrointestinal tract, biliary ducts, and pancreas. But it is quite possible that other sites of secretion exist. The brain, especially the basal ganglia and the area postrema, and the platelets are the other main sites where this substance is found. In neither of these is it thought to be a product of local activity; it has been suggested that the platelets act as a storage site and means of transport. In the dog, the maximum concentration of 5-HT is found in the hypothalamus which is considered to be the central representation of the autonomic nervous system. The high concentration of 5-HT in the area postrema is of interest in so far as this contains neuroglia only, and not true nervous tissue.

Having briefly mentioned the commonest sites of occurrence of 5-HT in the universe in general and man in particular, it pays to glance at its assumed mode of action. As has been said, the maximum concentration of 5-HT is found in the hypothalamus which is concerned with the central control of the autonomic system. Starting from physiological concepts and from observations of the behaviour of cats after stimulation of the hypothalamus, Hess concluded in 1954 "that two opposing systems, which he called ergotropic and trophotropic, integrate basic life functions ordinarily beyond voluntary control. These divisions, which are represented by definite parts of the brain stem, co-ordinate meaningful behavioural patterns by linking somatic and autonomic functions. The ergotropic system co-ordinates those mechanisms that physiologically belong to bodily work. Activation of this system stimulates the sympathetic nervous system, increases skeletal muscle activity, induces arousal and activates psychic states. The opposing trophotropic system integrates mechanisms that have a protective and assimilative function. Activation of this system stimulates

the parasympathetic system and decreases motor activity, sensitivity to external stimuli and a drowsiness akin to natural sleep."²

As to the local action of 5-HT in the gut, this substance, the continuous production of which is stimulated by the intra-luminal pressure of the intestinal contents, sensitizes the sensory nerve endings of Meissner's plexus and so initiates peristaltic movement. Now the clinical manifestations of carcinoids or argentaffinomas of the intestinal tract are notably fiery flushing of the skin after alcohol, tachycardia, bronchial asthma, and diarrhoea—effects which one would attribute to stimulation of the ergotropic system rather than the trophotropic system of Hess. The diarrhoea alone can be satisfactorily accounted for by the increased amount of 5-HT in the gut.

Is it possible in any way to link the above observations with the known action of *Bufo* in particular? And will it be possible to find some connection between the action of 5-HT and that of the other substances enumerated earlier which have been found to contain it? Have *Bufo*, *Sepia*, *Murex*, *Vespa*, *Tarentula*, *Urtica urens*, and *Macula urens* anything in common in their provings, and if so, is it of any significance, as even the most superficial reading of the *Materia Medica* shows a considerable overlap of a large number of remedies? Or is it perhaps because of the presence of such a substance as for instance 5-HT that the overlap exists?

In the chapter headed "Batrachia, Reptiles, Birds—Their Significance",³ H. Jaworski traces the development of the sudorific glands through the sting cells of polyps and octopuses as far back as the "harpoons and venomous darts" of protozoans. He also, in summoning up the significance of Batrachia in his vision and interpretation of evolution, says that they individualize cutaneous function. Embryologically, the skin and nervous system are derived from the same layer of cells—the ectoderm, and it is interesting to note that the presence of 5-HT is connected in the animal world with structures of ectodermal origin. Whether the venom of the toad is secreted by skin glands or salivary glands, their embryological origin is the same. Conversion of tryptophan to 5-hydroxytryptophan, which is the immediate precursor of 5-HT, was first shown in the venom gland of the intact toad.⁴ An immediate precursor of 5-HT is contained in the "venom" of *Bufo* which is a remedy not well proven. Kent, in his chapter on *Bufo*, stresses particularly that "most of the *Bufo* patients will be placid, passive, and slow". And Hess maintains that a definite slowing of activity is produced by stimulation of the trophotropic system. If Brodie is right in his interpretation of the effect of 5-HT on the trophotropic system, then a connection could be made between the action of *Bufo* and 5-HT. It would be most interesting to see whether 5-HT given in potency to provers would in fact produce a picture similar to *Bufo*. Can a mere chemical substance of however fine energy matter have the same effect as a secretion of an animal of such significance in H. Jaworski's evolutionary plan, of such significance in fairy tales and probably in dreams?

Again developmentally, at the stage when the embryo consists of only two layers of cells, ectoderm and entoderm, the latter would seem to arise by a process of invagination or interiorization of the former. In the toad, this slow, sluggish, horny skinned animal, the presence of 5-HT is connected with an excretion or secretion of ectodermal origin, while in man one of the sites of maximum concentration is of entodermal origin. Sluggishness is one of the keynotes of the remedy *Bufo*, it is the keynote also of the patient whom it might benefit. Is it too bold a step to connect skin disease, bowel disturbances, and disturbances of vegetative function, and look at them in the light of exteriorization and interiorization of function? And does the slowness in the psychic and emotional sphere come first, or is it the sequel to bodily dysfunction?

Can one justify the use of *Bufo* therapeutically in people who look like toads? Will a deeper study of this and related remedies give greater insight into the vast field of what is commonly called psychosomatic medicine? And will an approach to the nature of remedies along not one but many paths, circuitous though those might appear to be, have its own reward in the deeper understanding of their possible mode of action?

REFERENCES

- ¹ Harrington, Sir Charles, From the Opening Remarks of *5-Hydroxytryptamine, Proceedings of a Symposium Held in London on 1st and 2nd April, 1957*. Edited by G. P. Lewis, Ph.D., Pergamon Press, London, 1958.
- ² Brodie, B. B., "Storage and Release of 5-Hydroxytryptamine", *5-Hydroxytryptamine*, p. 61 ff.
- ³ Jaworski, Dr. H  lan, *Apr  s Darwin*, Paris, 1933.
- ⁴ Udenfried et al., *J. biol. Chem.*, **224**, 803 (1957); quoted in *5-Hydroxytryptamine*.

TOADS IN SHAKESPEARE

Shakespeare has twenty-four references to toads, of which the best known is:

"Sweet are the uses of adversity,
Which, like the toad, ugly and venomous,
Wears yet a precious jewel in his head."

As You Like It, II. i.

Caliban associates toads with beetles and bats for the purpose of cursing, and Macbeth's witches mix into their brew

"Toad, that under cold stone
Days and nights hast thirty-one
Swelter'd venom sleeping got."

Macbeth, IV. i.

Othello, in the first agony of his jealousy, exclaims

"I had rather be a toad,
And live upon the vapour of a dungeon,
Than keep a corner in the thing I love
For others' uses."

Othello, III. iii.

There are more toads in *Richard III* than in any other play, all expressive of disgust; and Ajax says

"I do hate a proud man, as I hate
The engendering of toads."

Troilus and Cressida, II. iii.

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