decreased enzymic activity induced by substrates has been noted by us with X-rays, ultraviolet light and ultrasonic waves (to be presented elsewhere), it seems possible that this may reflect a general effect which can provide a working hypothesis for certain aspects of poorly-understood problems such as tachyphylaxis, drug habituation, chemotherapy, fever and allergic phenomena. The administration of a drug, or of a substrate in a large excess, may result in increased destruction of an enzyme particularly at high temperatures and if other necessary components are not present at concentrations which will protect the enzyme. Under these conditions, either after resynthesis of the enzyme(s) or after removal of end products, the drug will be effective again (tachyphylaxis). Either enzyme binding, or destruction, or both, or slow resynthesis of the enzyme, may require higher doses to produce similar effects due to affinity considerations (drug habituation). It is well known that many drugs, for example, streptomycin, penicillin, certain sulphonamides and isoinazid can be more effective at lower temperatures. Fever might influence biological systems in an unsuspected manner. Examples in immunology possibly related to the phenomena under considerations, are the cold agglutinins and the higher precipitate obtained at 0 °C than at 37 °C in cross reactions.

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Enzymic oxidation of psilocine and other hydroxyindoles

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IT has recently been shown that the gill plates of *Mytilus edulis* L. contain an oxidase that acts on 5-hydroxyindoles, e.g. 5-hydroxytryptamine, bufotenine and 5-hydroxytryptophan; in the oxidation of these substances yellowish-brown pigments are formed.[1]

We have recently been able to compare the enzymic oxidation of bufotenine with that of its 4-hydroxy and 6-hydroxy analogues. The 4-hydroxy analogue of bufotenine is psilocine, a psychotropic amine naturally occurring in the fungus *Psilocybe mexicana* Heim,[2] where it is found together with its phosphate ester, psilocybine.

It was found that both hydroxyindoles were oxidized by the *Mytilus* preparation. The rate of oxidation of the 6-hydroxy derivative was similar to that of bufotenine; a faint yellowish-orange colour appeared during the reaction. With psilocine as substrate, oxygen uptake was more rapid than with bufotenine or with 5-hydroxytryptamine, and a blue colour appeared in the reaction. The rapid phase of the oxidation was over when about one atom of oxygen per molecule of added psilocine had been consumed. The contents of the manometer flask then showed a deep blue colour, with an absorption maximum at 625 mμ

We also had an opportunity of studying the *N*-1-methyl derivatives of both bufotenine and of psilocine. The 5-hydroxy compound was oxidized at about the same rate as bufotenine. The *N*-1-methyl derivative of psilocine was oxidized more slowly than psilocine itself, and the development of the blue colour was less rapid. These observations show that the substrates of the *Mytilus* oxidase

are not restricted to 5-hydroxy indoles. We therefore propose the name "hydroxyindole oxidase" for the enzyme.

The rapid oxidation of psilocine, together with the development of the deep blue colour, is of particular interest. It is suggested that in the enzymic reaction of the 4-hydroxyindole an *o*-quinonoid compound is formed. The oxidation of the 5-hydroxy and the 6-hydroxy indoles may lead to the formation of *p*-quinones.

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Cerebrospinal fluid and bradykinin release

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A RECENT investigation[1] showed a correlation between bradykinin release and the activation of plasmin in rat and bovine plasma. Various human body fluids contain an activator of plasminogen or its precursor.[2] Normal human cerebrospinal fluid was found to contain only the proactivator of the fibrinolytic system.[2] More recently Chapman and Wolff[3] showed that cerebrospinal fluid from patients with an active central nervous system (CNS) disease contracted smooth muscle or developed such activity when incubated with a bovine globulin fraction. Bioassay showed similar properties to vasodilator peptides[4] derived from plasma proteins, such as bradykinin[5] which is released by protease action. It became of interest to decide whether cerebrospinal fluid from patients with CNS disease contains sufficient amounts of protease to release bradykinin or whether the reaction involves activation of a fibrinolytic type.[6]

Cerebrospinal fluid from five patients* was investigated for protease activity using the synthetic substrates† benzoyl-1-arginine methylester (BAMe) and toluenesulfonylarginine methylester (TAMe) and the fibrin plate method.[8, 9] At most, only traces of protease activity could be detected with the synthetic subtrates. In one case, however, (multiple sclerosis) a protease/esterase activity was observed with 0·01 M-TAMe (no activity with BAMe) and 0·08 ml per ml of the cerebrospinal fluid in 0·02 M-phosphate pH 7·7. trypsin† (5 μg per ml), approximately ten times higher activity was obtained. When trypsin was added after incubation of the substrate with the cerebrospinal fluid no activity developed, showing that the substrate was used up and that although low this sample had a detectable

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