restrict its use for more than a very short time is another matter. These drugs are not like newly discovered antibiotics, the production of which is at first on a very small scale. They are simple compounds, easily manufactured. They are also easily administered, so that to the prospect of indiscriminate prescription has to be added even the possibility of self-medication. The only type of case in which their effect has so far been recorded is just that—the "hopeless"—on whose behalf demands will be most immediate, insistent, and urgent. We have therefore another situation, in a series which began with penicillin, where the distribution of a new drug must be the subject of serious anxiety and, it is to be hoped, well-considered control.

A.C.T.H. AND CORTISONE IN INFECTIVE HEPATITIS

The treatment of infective hepatitis is still far from satisfactory, and it is not surprising that both A.C.T.H. and cortisone have been tried in this condition. With any disease whose course is so variable and whose outcome so unpredictable as infective hepatitis it is difficult to assess the value of a new treatment unless a large series of adequately controlled cases is investigated. So far no such series has been reported on, though some interesting observations have been made. The most promising results were obtained by Webster.[1] Nine cases of hepatitis, including one of homologous serum jaundice and two of arsenical hepatitis, all of which were severely ill despite modern therapy, were treated with aqueous or oily extracts of adrenal cortex. Recovery in all was described as dramatic, and none had any signs of liver dysfunction when examined a year later. Encouraging reports have also come from Colbert and his colleagues,[2] who treated five acute cases of hepatitis with A.C.T.H. given by six-hourly injections of 25 mg. All five rapidly lost their anorexia and developed voracious appetites. Of perhaps still greater importance from the patient's point of view was the disappearance of pruritus, which can prove a most distressing symptom. A prompt fall in serum bilirubin was also recorded, but no definite change in liver size or tenderness. Most significant, perhaps, in relating these improvements to the effect of A.C.T.H. was a definite rise in the serum bilirubin in two cases when the injections were stopped, and a further fall when the treatment was restarted.

A less encouraging picture was drawn by Holmes and Percefull.[3] In a group of patients being treated for a variety of diseases they studied the effect of cortisone therapy upon the results of a series of liver function tests, and while they found no impairment of function attributable to the hormone they also saw no improvement in the two cases of hepatitis included in their series. In view of what is known of the effect of A.C.T.H. and cortisone upon protein, fat, and carbohydrate metabolism, and especially of the ease with which fatty infiltration of the liver is induced in the livers of animals treated with these hormones, it is both surprising and gratifying that no obvious adverse effects result from their use in hepatic disease. The liver plays an important part in the metabolism and inactivation of the adrenocortical hormones. Some steroids—oestrone, for example—are certainly inactivated in the liver, and evidence of hyperoestrinism can and does arise in some cases of hepatitis. Not so much is known about the metabolism of cortisone, but the unusual incidence of side-effects in all five of Colbert's cases strongly suggests that the normal inactivating mechanisms were here at fault.

Virus hepatitis is in the main a relatively benign disease. Two complications are to be feared—acute yellow atrophy, which is usually rapidly fatal, or the development of a chronic condition leading to cirrhosis. The incidence of acute yellow atrophy and the mortality in most epidemics are about 0.2 to 0.5%. To assess the value of a therapeutic agent by its effect upon mortality would therefore require a truly enormous controlled investigation. The incidence of chronic hepatitis, and its sequel cirrhosis, is probably higher than the mortality from acute yellow atrophy, but chronic hepatitis is much less readily identified. Consequently the great majority of investigators attempting to assess the value of any therapeutic agent in infective hepatitis have relied upon the timing of some well-defined clinical event, such as the duration of biliuria or raised serum bilirubin. Until a similar trial is undertaken with A.C.T.H. or cortisone it will be impossible to assess the value of any of these substances in the treatment of hepatitis. From the preliminary results already reported on small and uncontrolled series it can be safely concluded that the therapeutic activity of these new drugs is not remarkable and that an unusually large number of side-effects may be expected.

[1] *Ann. intern. Med.*, 1950, **33**, 854.
[2] *New Engl. J. Med.*, 1951, **245**, 172.
[3] *Ann. intern. Med.*, 1950, **35**, 608.

THE MECHANISM OF TASTE

Ever since the discovery of the taste buds nearly a hundred years ago, and the demonstration of their connexion with the glossopharyngeal nerve, they have been assumed to be the organs responsible for the sensation of taste. Taste buds in man are distributed mainly in the vallate fungiform and foliate papillae of the tongue

and never in the filiform papillae. The vallate papillae are mostly concentrated in a V-shaped area at the back of the tongue, with the apex of the V pointing backwards. Single taste buds also occur elsewhere, in the epithelium of the tongue itself or in the lining of the pharynx, in the palate and the epiglottis. Those which are associated with the papillae are, in the adult, present in the sides, never on the top of the papillae. In infants, however, there may be taste buds in this position on the top, and there are many more of them scattered through the buccal cavity, but they are lost as the child grows. There is no explanation for this diminution in numbers of buds with age.

The buds themselves are made up of two types of cells, which are referred to as "sustentacular" or supporting cells, and rod, hair, or gustatory cells. The former completely enclose the bud rather like the staves of a barrel, but they also occur in the inner part of the bud, where they are mixed with the gustatory cells. Although many workers were of the opinion that these cells were separate entities, Heidenhain,[1] among others, found all stages of gradation between them, and was convinced that they represented the one system of cells. There is a plexus of nerve fibres in the connective tissue beneath these buds, but surprisingly few fibres actually pass into the taste bud itself (intragemmal fibres), where they make contact with both types of cells. Most ramify in the epithelium around and adjacent to the buds (inter- and peri-gemmal fibres). The gustatory cells bear on their distal surfaces a single ciliary process sticking into the gustatory pore which opens to the exterior.

The method whereby this complicated cellular mechanism functions in taste is not known, but recent work by Baradi and Bourne offers a possible explanation. In 1948 Bourne[2] showed by histochemical methods that a phosphate-splitting enzyme (alkaline phosphatase) was located either in the taste buds or in the epithelium covering them in rabbit, bat, monkey, and man. Baradi and Bourne[3] subsequently carried out studies on the rabbit's papilla foliata, which is rich in taste buds, and found six phosphate-splitting enzymes in this region, together with an esterase (an enzyme which splits simple esters) and lipase (an enzyme which splits long-chain fatty acids). By adding small quantities of substances with well-defined tastes to the substrate mixtures used in demonstrating these enzymes, they secured inhibition of the activity of some of these enzymes and enhanced activity of others. This led them to suggest that the mechanism of taste depends upon the differential inhibition or stimulation of enzyme systems in the taste buds and the neighbouring epithelium. Since so many of the enzymes are concentrated not in the taste buds but in the epithelium near them, and since this epithelium is richly supplied with nerves, Baradi and Bourne have suggested that perception of taste is not wholly a function of the taste buds but is partly a function also of this epithelium. This idea is taken further by the anatomical and clinical observations of Dr. Wilfred Harris in his article in our opening pages this week. He finds that lesions of the fifth cranial nerve may impair the sense of taste, which is usually ascribed only to the seventh nerve, and he believes that tactile, painful, and thermal stimuli from the tongue and palate also contribute to form the individual's taste judgments.

Baradi and Bourne point out that the enzymes they studied are distributed in six different sites in and around the taste buds. Since any of the enzymes in these sites is capable of being inhibited, accentuated, or unaffected by a particular tasting substance, and since this can happen in any one of the six sites, it means that each substance being tasted can produce a particular pattern of nerve stimulation according to what it does to a particular enzyme in a particular site. (Enzyme activity in the neighbourhood of a nerve fibre is assumed to cause a nerve impulse.) It can be worked out that this mechanism can thus produce 2,160 different nerve patterns, in other words it can be used to appreciate that number of different tasting substances—a hypothesis that would make the old conception of four basic tastes out of date.

This mechanism can also explain why substances of widely differing chemical nature can have the same or similar tastes. Since the distribution of many of these enzymes overlaps, inhibition (or otherwise) of different enzymes at the same sites by different substances will have the effect of producing the same pattern of nerve impulses which the brain will interpret as the same taste. It is of interest that these enzymes are also present in the olfactory mucosa, a fact which supports the conception of the similarity between taste and smell.

1 *Arch. mikr. Anat.*, 1914, **85**, 305.
2 *Nature, Lond.*, 1948, **161**, 445.
3 *Science*, 1951, **113**, 600; *Nature, Lond.*, 1951, **168**, 977.

AMINE OXIDASE

The earlier physiologists recognized that the sympathetic nerves, which accelerate the heart and mobilize our bodily resources for "fight or flight," are generally opposite in function to the parasympathetic, which adjust our secretions and call forth the responses appropriate for the more pleasurable activities of eating and repose. Sir Henry Dale brought the vegetative nervous system into sharper definition with his brilliant concept of the division into groups of adrenergic and cholinergic nerves, which transmit their impulses to the muscles and glands by liberating the specific transmitter substances adrenaline and acetylcholine respectively. That gave a rational explanation of the selective action of atropine, which blocks the access of acetylcholine to the end-organs in the glands, thereby inhibiting salivation and drying the tears. It also explained the curious anomaly of the sweat glands, which are innervated by nerves derived anatomically from the sympathetic nervous system but which respond to acetylcholine, since these nerves are cholinergic in function.

The story of parasympathetic nervous activity was extended by the discovery of cholinesterase, an enzyme that destroys acetylcholine liberated at the cholinergic

1 Blaschko, H., Richter, D., and Schlossmann, H., *Biochem. J.*, 1937, **31**, 2187.
2 Richter, D., ibid., 1937, **31**, 2022.
3 *J. Physiol.*, 1938, **94**, 87.
4 *British Medical Journal*, 1952, **1**, 784.

nerve endings, thereby controlling the responses of the organs supplied by these nerves. The effects of cholinesterase inhibitors such as eserine and "prostigmine" could be attributed to their preventing the destruction of acetylcholine: these drugs thus mimic the effects of stimulation of the parasympathetic nerves. That raised the question whether there is a corresponding enzyme that destroys the transmitter substance of the sympathetic nerves. The first evidence that such an enzyme might in fact exist was obtained by a group of Cambridge workers, who showed that the tissues contain an amine oxidase that inactivates adrenaline by oxidizing it in the side-chain to form methylamine and an aldehyde.[1 2] They showed further that this enzyme is inhibited by ephedrine; and their suggestion that the amine oxidase might act physiologically by destroying the transmitter substance at the adrenergic nerve endings received important support from the work of Gaddum and Kwiatkowski,[3] who found that ephedrine increased the constrictive effect of sympathetic stimulation on the arterioles of the rabbit's ear.

It is now known that the sympathetic transmitter substance is not adrenaline, but that it consists mainly of a closely related substance *nor*adrenaline (which is adrenaline minus the methyl group). This has helped to clear up certain anomalies that previously prevented acceptance of the view that the amine oxidase destroys the sympathetic transmitter. Burn and his colleagues have shown that *nor*adrenaline is inactivated more rapidly than adrenaline by the amine oxidase, and they have now collected an impressive array of evidence (summarized in last week's *Journal* by Professor Burn[4]), all of which supports this view of the function of the amine oxidase in relation to sympathetic activity. The amount of amine oxidase in the tissues decreases after denervation, and this can explain the observed changes in the sensitivity to *nor*adrenaline. The amount of enzyme in the blood vessels and in the liver varies with changes in thyroid activity and in such a way as to give a feasible explanation of the greater sensitivity of thyroid-treated subjects to the hypertensive and hyperglycaemic effects of adrenaline. These observations point to the importance of amine oxidase in the control of the blood pressure and indeed in all the functions mediated by the sympathetic nervous system.

PULMONARY TUBERCULOSIS AND PREGNANCY

In recent years many authors have expressed the view that pregnancy has very little effect on the course of pulmonary tuberculosis in the mother. The swing of the pendulum of opinion in this direction began after the 1914–18 war, and it is now widely believed that pregnancy has less importance than the extent of the disease and the adequacy of its treatment. In this issue Dr. J. R. Edge presents the results of a survey of 462 women of child-bearing age who were admitted to the Brompton Hospital during the years 1945 and 1946, and whose course was followed until the end of 1950. Among the questions which he investigates is the time relation between the diagnosis of pulmonary tuberculosis and parturition. It is sometimes held that the disease becomes manifest sufficiently often in the early weeks after delivery to make it likely that the illness was activated by pregnancy. He shows that this activation is unlikely, for the number of women in his series diagnosed within three months of parturition is not greater than could be ascribed to chance. In examining the effect of pregnancy on pulmonary tuberculosis in his patients Dr. Edge reviewed the progress of 47 who completed 54 pregnancies and whose course was followed afterwards for periods of between one and five years. There were also 18 patients in whom 20 pregnancies were terminated surgically. Both in patients with active and inactive tuberculosis it did not seem that the course of the disease was much different whether the pregnancy was interrupted or allowed to go to term. He draws the conclusion that there is probably no indication for therapeutic abortion, and in addition he believes that the course of the disease in his series of patients was not affected by the pregnancy, whether this was terminated or allowed to continue.

Another very recent study by Cohen and his colleagues[1] follows the course over periods of between five and twenty years of 149 tuberculous mothers with 401 full-term pregnancies. These authors come to the general conclusion that neither gestation nor the first post-partum year has any deleterious influence on the course of tuberculosis. They describe the methods of treatment used in their pregnant patients, and consider that the indications and contraindications for pneumothorax, surgical collapse of the lung, and excision are the same as for non-pregnant tuberculous patients. In their view modification of treatment because of associated pregnancy is rarely necessary. However, they advise that the third trimester of pregnancy should not be disturbed by a major operation because of the danger of inducing premature delivery. They use streptomycin during pregnancy for the same indications and in the same dosage as in the non-pregnant patient: two pregnant women received 1 gramme of streptomycin daily for 45 days without damage to the child in either case.

It seems clear that with quiescent or arrested disease therapeutic abortion is not justified if the patient can be supervised. Patients with disease likely to be controlled by treatment should continue their pregnancy and be treated in the most effective way possible. In some it may be thought unlikely that the disease will be controlled even with the thorough application of modern therapy. In such circumstances, if arrangements can be made for the child to be looked after, it may be reasonable to continue the pregnancy, but the decision will often require careful judgment on the part of the patient's doctor. In any case, if the pregnancy has lasted longer than three months it is best to allow it to continue: the question of termination must be decided before the end of the first twelve weeks.

Sir Russell Brain was re-elected President of the Royal College of Physicians of London on April 7. He was first elected President of the College in 1950.

1 *Amer. Rev. Tuberc.*, 1952, **65**, 1.