the involution of the metastases where colloid accumulation is conspicuous is quite evident. It seems, therefore, that these adenocarcinomas of low grade malignancy are still responsive to changes in the level of thyrotropic hormone. Judging from the histological appearances we would predict that thyroid medication if given earlier would have inhibited the development of these growths and their metastases, an effect which might have clinical application in certain cases of human thyroid malignancy. The marked tendency of the tumours here described to invade veins is characteristic of thyroid adenocarcinoma in human pathology, and the occurrence of masses of tumour cells lying within the blood vessels is frequently observed in human material. The occurrence of metastases in the lungs developing from tumour cell emboli in the branches of the pulmonary artery is therefore to be expected.

We believe that the production of these thyroid tumours is due, not to any direct carcinogenic action of the thiourea administered, but rather to the excessive and prolonged stimulation of the thyroid epithelium by the thyrotropic secretion of the pituitary. This action would be analogous to the specific production of breast tumours in susceptible animals by the administration of excessive amounts of oestrogen.

SUMMARY.

1. In thirty rats in which thyroid tumours had been induced by administration of thiourea for a period of nearly two years, two animals were found at autopsy to have malignant thyroid tumours.

2. The malignant nature of these thyroid tumours was evidenced by their invasion of the thyroid veins, and by the presence of numerous metastases in the lungs.

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TASTE AND SELECTION OF FOOD IN HYPOGLYCAEMIA.

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RICHTER and Campbell (1940), Richter (1942), Richter, Schmidt, jun., and Malone (1945) have shown that when experimental animals are allowed to select their diet from a series of foods, they choose in accordance with the constituents and concentrations in the body fluids; in other words, they try to maintain what Claude Bernard called a constant internal environment necessary for the maintenance of life. Richter has also shown that this self-regulatory activity depends on the sense of taste. The objections to applying the self-selection technique as used by Richter to man are obvious: conditioning by upbringing during the long infantile period; by regional feeding habits;

by the conventions of the table and by self-control, as well as by personal predilections, tend to impede self-regulation in human beings and make it less predictable. Richter *et al.* (1945) also speaks of man's defective taste mechanisms. In an emergency like hypoglycaemia, however, one would expect cultural habits and personal factors to be of little weight in comparison with the vital demands of the body.

The behaviour of patients undergoing insulin treatment, described Sakel (1938) as "hunger riot," seems to confirm that, at a certain stage of hypoglycaemia, schizophrenics break all rules and conventions in their overwhelming craving for carbohydrates. Hunger riot, however, far from being a regular feature among hypoglycaemic patients, is rather infrequent in the routine treatment of schizophrenia. Another common finding inconsistent with self-regulation is the diabetic who, when hypoglycaemic through an overdose of insulin, angrily refuses to take sugar offered by the people around him, since he lacks insight into his abnormal condition. While he still seems conscious and aware of his surroundings, his self-regulation is apparently deficient. The effect of hypoglycaemia on cortical function and consciousness has, of course, to be taken into account whenever self-regulation is tested in this condition. In view of these contradictory observations, it seemed worth while to approach the subject experimentally, using the self-selection technique with the object of finding out whether and, if so, how far self-regulation operates in the hypoglycaemic patient. If its operation was found to be the general rule, individual deviations from it may deserve closer analysis; the corresponding subjective taste sensations unknown in animal experiments would be worth while studying; and finally, one could try to interfere with self-regulation by using substances of deceptive taste or distractive smell.

The present paper is based on about 250 experiments arranged under the above propositions.

METHOD AND MATERIAL.

In the main series of tests the patient was asked to take small sips from five glasses of colourless liquids marked A, B, C, D and E, and to describe their taste. He was also asked which of the liquids he would like best for a long drink. If a subject was in doubt about his final preference, he was allowed to re-taste the whole series, or a couple of glasses, before making up his mind. Notes were made of the subject's reactions towards each liquid and of his final choice, and blood glucose determinations were made at the time, using the method of King, Haslewood and Delory (1937). In retesting the same individual care was taken that the order of the five solutions was not the same twice running; in fact, the order was varied on each testing day.

The five solutions used were as follows: water, 5 per cent sucrose, 30 per cent sucrose, 0·5 per cent sodium chloride, and saccharine. The saccharine solutions were made to equal, as nearly as possible, the sweetness of the 30 per cent sucrose solution. This was not altogether easy, since the sweetness of saccharine does not follow a simple rule, and becomes proportionately less sweet as the concentration increases. The low solubility of the substance and the varying degree of sweetness of various samples are additional complications. Each sample was made up immediately prior to use, and was standardized by

experimental tasting by the same experimenter, so that in each series saccharine sweetness was as nearly as possible identical with that of the 30 per cent sucrose solution. The temperature of all liquids was kept equal with that of tap water.

The subjects of the experiments were physically healthy individuals between the age of 17 and 45, undergoing Sakel's insulin therapy for early schizophrenia. It was considered unlikely that their mental illness would interfere with the experiments. Schizophrenics sometimes refuse food, others devour everything they can get hold of regardless of taste. Such patients were not included among our subjects, and cases of catatonic stupor and similar states, in which clearness of consciousness was doubtful, were also left out. Some peculiar predilections in our series may be put down to perversions of taste due to the mental condition. On the whole, however, it can be maintained that schizophrenia does not affect the sense of taste and that our patients' behaviour in these tests was not essentially different from that of normal subjects in hypoglycaemia.

The experiments were made in various stages of hypoglycaemia, covering all glucose levels from fasting to that of incipient hypoglycaemic coma. By proper timing of the experiment during the progressive hypoglycaemia we succeeded in obtaining a sufficient number of results even within the lower range of blood glucose. As long as the patient understood the instructions, could hold the glass, describe the taste and express his preference, his case was included even if he seemed slightly drowsy.

The following example may illustrate the procedure under such conditions.

Case R—, 19.5.44.

7.30 a.m. : 100 units insulin.

10.35 a.m. : Sweating, narrow pupils, but seems quite clear.

A. (saccharine) : " Good."

B. (NaCl) : " Too salty."

C. (5 per cent sucrose) : " Better than A."

D. (H_2O) : " No."

E. (30 per cent sucrose) : " I like E. Prefer it to A. C is probably the best—can I try again ? " Tastes C, E, and A.

" E, I think, is better than C or A."

Blood glucose 23 mg. per 100 ml.

RESULTS.

The main series of experiments consisted of 202 observations in 100 patients. The first result showed that the preference for the 30 per cent sucrose solution as a long drink was definitely related to the blood glucose level. Above a level of 50 mg./100 ml. the proportion of subjects preferring this solution was low, but below this level the proportions were reversed. In Figs. 1 and 2 illustrating this result the experiments are divided into groups according to the blood glucose level, each group covering a range of 5 mg. glucose per 100 ml. Three experiments where no decision could be obtained were omitted. Fig. 1, giving the absolute numbers of experiments, shows those preferring 30 per cent glucose above, those choosing one of the other liquids below the line. It conveys an idea of the number of experiments in each group. In Fig. 2, the same preferences are given in percentages of the group and plotted against the blood glucose group.

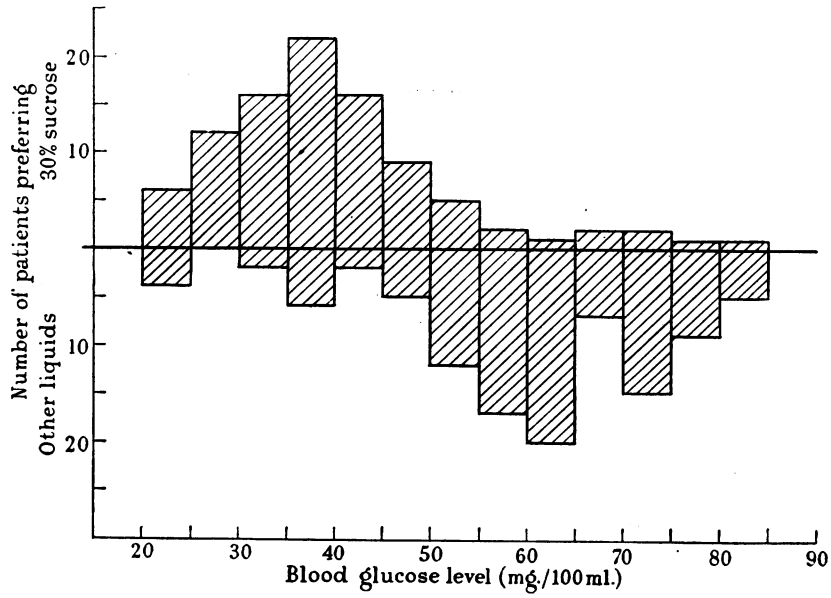

FIG. 1.—Preference (actual numbers) for 30 per cent sucrose in relationship to blood glucose level.

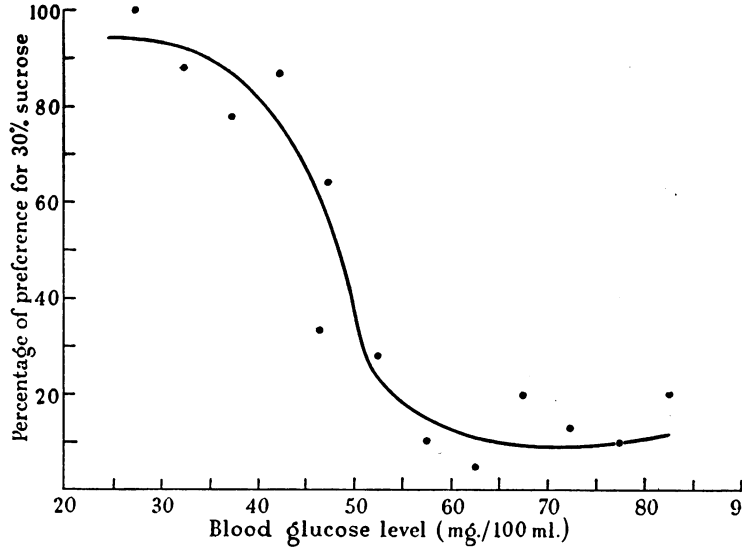

FIG. 2.—Percentage of Preference for 30 per cent sucrose in relationship to blood glucose level.

The great majority of subjects whose blood glucose level was over 50 mg. per 100 ml. rejected the 30 per cent sugar solution as too sweet, while only a small minority of those with blood glucose below this value preferred one of the other liquids to this solution.

The result leaves no doubt that the taste in hypoglycaemia is governed by the principle of relf-regulation and that the influence of conditioning factors is negligible. The change of taste was found to occur at almost one point of the blood glucose scale.

Having thus established the validity of the general principle of self-regulation in human hypoglycaemia, we can now consider the results in greater detail.

30 per cent sucrose solution.—This was preferred to other liquids on 95 occasions ; only in eleven of these tests, performed on nine subjects, was the blood glucose level above 50 mg./100 ml. Five of these results came from three patients who showed other abnormal reactions. They will be discussed later in the paragraph on saccharine. Subjects repudiating 30 per cent sucrose described it as " syrupy," " sweet and oily," awfully sweet," " very sweet syrup," etc.

5 per cent sucrose solution.—Many subjects recognized the similarity of the two sucrose solutions. 5 per cent sucrose was chosen as a long drink 28 times ; the blood glucose was 19 times above the critical level. In instances below this level its taste was described either as " mild or weak sweetness," " water with a wee bit of sugar," or as " watery," " plain," " rather dull," or " not much taste."

Omitting equivocal replies, 175 judgments on this solution were grouped according to the three criteria " sweet," " slightly sweet " and " tasteless." The percentage of " tasteless " was significantly higher in cases of blood glucose below 50 than in cases above this level (36 against 18 per cent), while " sweet " was higher above the critical level (19 against 32 per cent).

Water.—There is considerable loss of water during hypoglycaemia. Sweating is often the first sign of the vagotonic effect of insulin, followed by excessive secretions of saliva and of gastric juice ; bronchial and lacrymal secretions are also increased. Complaints of thirst are frequent. Water was, in fact, preferred to the others and was chosen as a long drink in approximately one quarter of the experiments (51). In only nine instances was the blood glucose below 50 mg. per 100 ml. Water was recognized in the majority of cases or described as tasteless.

NaCl solution.—Because of the simultaneous loss of chlorides by perspiration and gastric secretion, preference was expected for the 0·5 per cent salt solution. Only on one occasion, however, was it chosen as a long drink with a blood glucose of 70 mg. per 100 ml. The subject described its taste as " bitter " and at the same test the taste of water " like soda." Perversion of taste was suspected but it was found that the same subject had chosen 30 per cent sucrose when his blood glucose was 28 ; he then called the taste as salt " terrible." Aversion towards the salt solution was widespread. Disgusted grimaces, expressions like horrible, awful, unpleasant, were most frequent in the lower range of blood glucose. The description " bitter " occurred 16 times.

However, in 138 out of 199 experiments (three subjects were unable to give any description) the solution was correctly described as salt, salty, brine, etc. Only one patient maintained on two occasions that he liked the salt solution, although this did not influence his final choice which followed the general rule.

Saccharine.—Saccharine was included in the series of liquids for the following

reasons: The compounds which give rise to a sweet taste may be divided into two classes, the first of which contains a relatively large number of free hydroxyl groups, polyhydric alcohols and carbohydrates, e.g. glycerol and sucrose. The degree of sweetness is, to some extent, related to their food value. The second class consists of benzene derivatives in which the degree of sweetness is not related to nutritional value; an example of this class is saccharine. One of the problems of self-regulation is whether the hypoglycaemic subject will be able to distinguish between the "natural" sweetness of the first class of compounds and the "artificial" sweetness of the saccharine group.

In 24 cases saccharine was chosen as a long drink and preferred to the other liquids. Only three of these had, however, at the time a blood glucose level below 50 mg./100 ml. This seemed remarkable, considering that the sweetness of the saccharine was intended to be as close as possible to that of 30 per cent sucrose. In other words, self-regulation could not be deceived by the sweet taste of saccharine, a substance unable to raise the lowered blood glucose level.

It seemed of interest to group the instances in which saccharine was not recognized as sweet according to the blood glucose levels. Out of 45 cases denying sweetness of saccharine 33 had a blood glucose below 50 mg./per 100 ml. This can be interpreted as protection against the "artificial" sweetness where it is most needed. On the other hand, in 157 tests (78 per cent of the total) saccharine was recognized as tasting sweet, sweetish, sugary, too or slightly sweet, in 120 of these without further comment. A relatively small number of subjects (22) took notice of the admixture of the different taste saccharine has for most people, with expressions as follows: "sweet, but something else," "sweet and bitter," "sugar and salt." The verdict "bitter" occurred 13 times, salty only twice. Two subjects described the taste as "synthetic sweetness" and two others recognized the taste as that of saccharine.

Although only preferred to the other liquids in 12 per cent of the total, the majority of the subjects did not loathe saccharine. Unsolicited dislike was voiced 16 times, but 28 times the taste was spontaneously described as pleasant.

Detailed analysis of the 24 experiments, in which 18 subjects preferred saccharine to the other liquids, revealed that six subjects selected saccharine on two occasions; when two of these subjects were given one or more further tests their preferences seemed to follow the general trend. The same holds true of five subjects, who selected saccharine only once, but made their choice conforming to standard on earlier or later occasions. In three subjects, however, some perversion of taste could be suspected; they preferred saccharine at a blood glucose level of 49, 53 and 55; in repeated tests the same subjects selected the concentrated 30 per cent sucrose solution at even higher blood glucose levels, two of them on two different occasions (see paragraph on 30 per cent sucrose). Here a personal factor seemed to interfere with the self-regulatory mechanism; but no connection with the schizophrenic psychosis could be discovered.

To sum up, saccharine did not interfere with the prevailing principle of self-regulation, and the predilection for the sweet taste did not become unselective with the lowering of consciousness through hypoglycaemia.

Odour.—Some preliminary experiments were designed to test the effect of odour on self-regulation. They consisted of two series undertaken in the same subjects.

In the first part a series of aromatic extracts (peppermint, "strawberry," aniseed, cinnamon and clove), made up in 2·5 per cent sucrose solution, were presented to subjects in a fasting condition. The reaction to each solution and an expression of preference was obtained, and at the same time a blood glucose determination was made. Later the same subjects were re-tested in a condition of hypoglycaemia (blood glucose below 50). This time the five original solutions (5 per cent sucrose, 30 per cent sucrose, saccharine, water and 0·5 per cent sodium chloride) were used, but to all, with the exception of that containing 30 per cent sucrose, were added the aromatic substance for which a preference had been expressed in the first test. The subjects' reactions to the five solutions, the expression of preference and the blood glucose level were duly noted.

The results showed that in many cases the subject had a strong liking for one or other of the aromatic "flavours" when the blood glucose was normal; but that when in a state of hypoglycaemia the universal preference was for 30 per cent sucrose solution, despite the fact that this solution alone did not contain the preferred flavour.

DISCUSSION.

In an earlier paper one of the authors (Mayer-Gross, 1941) put forward the hypothesis that the spontaneous movements of the mouth and face in hypoglycaemia are produced by excitation of areas in the central nervous system connected with food intake. Deprived of carbohydrates, the principal fuel, the remaining energy of the central nervous system is concentrated on parts which normally subserve the removal of such an emergency.

The present experiments were carried out in an earlier stage of hypoglycaemia before oral and facial movements had made their appearance. They confirm the predominant craving for carbohydrates. At one point of the blood glucose scale this becomes so great that the normal dislike for the excessive sweetness of a 30 per cent sucrose solution is reversed into a preference for this liquid. The hypoglycaemic subject not only chooses the solution best suited to replace the glucose deficit, but also discriminates between two compounds of equal sweetness, where one is able to replace the loss of glucose and the other unable to do so. The discrimination is sharpest where the need is greatest. Loss of water and of chlorides due to hypoglycaemia have no influence on the subject's choice, which is solely governed by the emergency of the carbohydrate metabolism. Odour has no effect on the subject's preference.

These findings are well in agreement with the theory of self-regulation, which explains the purpose underlying the subject's behaviour.

The limitations of a theory of this kind become apparent when insight is sought into the mechanism of the behaviour. The explanation of this mechanism must be based on Richter's findings that self-regulation depends on intact taste perception. Below a critical blood glucose level the sense of taste for sweetness is obviously depressed. Only half of the subjects recognize a 5 per cent sucrose solution as sweet at all; almost three-quarters of the subjects, not recognizing the sweetness of saccharine, had a blood glucose below the critical level. The depression of taste perception affected sweet taste only; salt and bitter tastes (the latter tested in experiments with phenyl-thiourea, not reported in this paper) appeared undisturbed. As it is generally assumed that special receptors of the tongue react to only one taste (Moncrieff, 1944), such as sweet,

and not to sour, bitter or saline, a specific depression of one type of receptor seems possible. Further investigations on this point, using threshold solutions, seem desirable.

The second problem is raised by the finding of a critical level in the region of blood glucose 50, below which the sweet taste perception becomes depressed. We have previously suggested (Mayer-Gross and Walker, 1945) that the glucose level of 10–15 mg./100 ml. is the critical level for the specialized function of cells in the cerebral cortex. It may well be that the level of 50 mg./100 ml. represents the critical level for the function of the taste buds of the tongue concerned with the sense of sweet. The function is not entirely lost at this level, but a definite depression of activity occurs.

The third problem refers to the apparent refinement within the sweet taste range, enabling the subjects to distinguish between a 30 per cent solution of sucrose and an equally sweet solution of saccharine. Several explanations are possible: one is that, owing to the depression of the sweet taste component in saccharine, the minute admixture of bitter or metallic taste, for which perception is undisturbed, comes to the fore and facilitates discrimination—especially below the critical blood glucose level.

A second possible explanation makes use of the different physical properties of the two solutions: (*a*) sucrose is more viscous than the saccharine solution, and will therefore be washed off the less quickly; (*b*) as concentration of solids in the 30 per cent sucrose solution is great, their diffusion into the tissue of the tongue is likely to be greater than in the case of the saccharine solution, where the concentration of solids is small; (*c*) as the specific gravity of saccharine is lower than that of the sucrose solution, the latter will exert greater pressure on the highly sensitive touch receptors of the tongue, which may facilitate discrimination. These differences in physical properties are, of course, the same whatever the level of the blood sugar. If, however, we accept the theory of the depression of function of the taste buds for sweet below a blood glucose level of 50, it is possible that at the depressed level of activity subsidiary factors of this kind play a greater part in the perception as a whole, and favour the choice of the sugar solution.

The results furnish no explanation of the observations at variance with self-regulation, which we mentioned in the introductory remarks—namely, the infrequency of " hunger riot " in insulin treatment, and the occasional intractability and lack of insight of hypoglycaemic diabetics. To account for these observations one will have to resort to the general depression of the cerebral cortex manifesting itself in apathy, lack of spontaneity, or emotional impassiveness. Such symptoms naturally become imperceptible if the investigator elicits answers from the subject, as in our experiments.

The relatively rigid experimental procedure may also be responsible for the poor yield of information on personal predilections and individual differences. On less than ten occasions—some mentioned under saccharine—an abnormal reaction could be suspected to be of this nature or, perhaps, influenced by the underlying psychosis.

SUMMARY

The paper is based on 202 experiments carried out in 100 subjects with the object of testing self-regulation in different stages of hypoglycaemia. The subject

was offered a choice of five liquids: water, 5 per cent sucrose, 30 per cent sucrose, 0·5 per cent sodium chloride and saccharine; his preference, judgment of taste and other reactions were noted and his blood glucose determined.

The most important result was the preference for 30 per cent sucrose solution below the blood glucose level of 50 mg./100 ml. and the rejection of it above this critical level.

Other findings, such as the judgment of sweetness for 5 per cent sucrose and saccharine, were also found related to the blood glucose level. Saccharine, although of equal sweetness with 30 per cent sucrose, was rejected below the critical level.

Loss of water and chlorides during hypoglycaemia had no influence on the selection of liquids; nor had odour, as demonstrated in special experiments.

The results are discussed in the light of the principle of self-regulation; but an attempt has been made also to explain the mechanism of the reactions in terms of the physiology of taste perception.

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THE EFFECTS OF LEWISITE AND OF LEWISITE OXIDE ON LIVING CELLS *IN VITRO*.

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THE experiments described below formed part of a research on the action of vesicants on living cells which was done at the Strangeways Research Laboratory for the Chemical Defence Research Department, Ministry of Supply, between 1939 and 1944.

Tissue cultures were grown *in vitro* under conditions which allowed the lewisite either to be applied to them superficially, or to be incorporated at known concentrations in the clots in which the cultures were growing. The effects on individual cells could be studied by continuous observation of the living tissue on a microscope kept at body temperature and equipped with a specially modified Mark VI service respirator, in which a 'blind' eye fitted over the

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