REGULATION OF FOOD AND WATER INTAKE : CONFERENCE REPORT

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IV International Conference on the Regulation of Food and Water Intake was held in Cambridge, U.K. on August 2-6, 1971. This was a multidisciplinary conference and was attended by principal workers in this and the related fields from all over the world. The Conference was supported by grants from the British Physiological Society and the British Nutrition Foundation, and had the status of a Satellite Symposium of the XXV International Congress of Physiological Sciences.

First Session : Orosensory and Gastric Factors

Cabanac (University of Claude Bernard, Lyon) reported his studies in which a previous ingestion of 50 *g* glucose, orally or by intragastric intubation, converted the pleasant taste of sweet solutions into an unpleasant taste in fasted healthy subjects. A gastric load of the same amount of glucose (50 *g*) did not produce such effect in undernourished healthy subjects with decreased weight or in overnourished obese individuals. These and other observations suggest the presence of an internal referral system of some "set points" for the sense of taste and olfaction with relation to an individual's body weight. In obese or in undernourished individuals, who are otherwise healthy, it seems that these referral points are set at higher levels. Grinker, Smith and Hirsch (Rockefeller University, New York) however, were not able to detect any difference in taste preference between obese and normal subjects using a criterion-free sucrose detection procedure. DiBella (Modena University, Italy) demonstrated a significant increase in food intake of the rat when lingual and glossopharyngeal nerves were cut at the back of tongue signifying inhibitory input from receptor areas of the tongue. Adrenalectomy in these animals, led to inhibition of food intake. This latter effect was dependent on salt intake which if increased, led to the same amount of food ingestion as the control rats. Kissilef (Rockefeller University, New York) reported that oropharyngeal sensations are much more important for maintaining adequate water intake in adrenalectomized rats and appear essential for maintaining long term saline intake even when selection and identification are minimized. Sodium taste, thus, is an innate reinforcer which is necessary to sustain increased sodium intakes in animals in which sodium need exists. Jayaraj (London) and Sharmas (Bangalore) described the histology and neurohistology of taste buds in starved frogs and found significant degenerative changes. Holmes (Colorado Medical Centre, U.S.A.) reported the differences in salivary compositions of normals and uremic patients admitted in the hospital for dialysis and kidney transplantation, and suggested that these differences affect their taste, capacity to swallow and also therfore, the fluid and food intake. Gutman and colleagues (Jerusalem, Israel) reported that of the various salivary glands, submaxi-

llary were the ones whose extirpation reduced spontaneous drinking and drinking induced hypovolemic stimulation, but produced a significant increase of saline preference. Wat deprived rats had less ATP-ase activity in the submaxillary glands than in the parotids. Besid a renin-like activity was discovered only in the submaxillary glands. These distinguishing feat es, therefore, determine the differences between the effects of submaxillary and parotid glan on water intake. Forsander (Helsinky, Finland) reported that by the method of selective bre ing, a strain of rats can be obtained which will prefer alcohol over water. Threshold of alcoh diuresis in these animals was very high when compared to the water-drinking rats. La (College de France, Paris) demonstrated that bilateral transection of olfactory pathways prod ed a pattern of food intake in rats which resembled the feeding pattern in rats recovering fr lateral hypothalamic lesions.

Davis (University of Illinois, U.S.A.) and Campbell (University of Sussex, U.K reported that the amount of time that the rat spent on drinking considerably increased successive days (upto 4 days) when stomach contents were simultaneously removed through stomach fistula. With successive removals of stomach contents the rate of drinking al registered an appreciable increase. This is in favour of Le Magnen's hypothesis that the pos ingestive satiety signals serve as unconditioned stimuli for oral conditioned stimuli. Takeshim (Chiba University, Japan) reported his studies of the afferent unit discharges of fibres innerva ing various parts of the stomach. Two types of fibres were demonstrated: (1) Discharges fibres from antrum and lesser curvature corresponded with changes in gastric volume an peristalsis. These were considered to carry information about changes in gastric tension. (Discharges in fibres coming from cardiac portions corresponded only with the changes i gastric volume and were considered to carry information of stretch changes of the stomach.

Second Session : Short Term Regulation

Collier (Rutgers University) emphasized the role of environment in determini the pattern of regulatory mechanisms and classified various patterns of regulation of foo intake from the ecological point of view. Thomas (Massachusetts, U.S.A.) investigate the effects of altered meal size and reported that in normal rats with ad lib facilitie if the meal is immediately followed by gastric infusion of extra diet, the intake is regulate through a sharp decrease in the frequency of meals. The hypothalamic hyperphagic rats to responded by increasing the frequency of their meals, when meal size was reduced throug gastric fistula. Thus, although increased meal size is an important factor for increased foo intake in hyperphagic rats, this does not seem to be a causal factor in the mechanism underlyin hypothalamic obesity. Borer (La Jolla, Calif., U.S.A.) reported that greater the number of an size of crabs offered to the octopus, bigger is the size of meal taken by the octopus suggestin that meal size of the octopus is not regulated but is merely influenced by the environment The octopus, it seems, regulates its food intake more on the long term basis than on the sing meal size. Brown and colleagues (Sheffield, U.K.) reported that when the breeder rats wer shifted to various types of experimental cages, their food intake was suppressed but the growth curves were not affected when compared with the controls. Levitsky (Cornell University

U. S. A.) reported that the meal size in rats was not only affected by the type of diet they ate but also by the amount of effort involved in procuring the meal. Meal size increased proportionately with the increase in effort, and so did the premeal interval. Peret and colleagnes (Bellvue, France) consider it unlikely that protein intake is the "zeitgeber" for appetite because in these experiments, the spontaneous rhythm of food intake had no temporal relation with protein feeding and existed even in the absence of proteins. Glycaemia, except for a slight elevation at the end of feeding remained stable throughout the 24 hour period. Prins and Wiepkma (Haren, Netherlands) described the differences in meal patterns of rats and mice as recorded by automatic registration methods supplemented by visual observation. In both species food intake per unit time increased during the initial period of meal taking suggesting the possibility of positive feedback to the "hunger centre" stemming from the ingested food.

Donovick, Bright and Hunter (New York State University, U.S.A.) showed that the rats with septal lesions ate and drank more during the night when compared with the controls. When the light cycle was reversed, the lesioned animals were slower to bring about the phase shift with the light-dark schedule. Stephen and Zucker (University of California, Berkley) demonstrated an immediate and complete suppression of ad lib water consumption when rats were switched from a 12:12 hour light-dark cycle to one of continuous illumination. Such a suppression was abolished on interrupting the inferior accessory optic tracts by lesioning the median forebrain bundle, but not by interruption of primary optic tracts by making lesions in the lateral geniculate bodies. Rats in the medial forebrain bundle lesions readily mastered the light-dark visual discrimination problems whereas the rats with lateral geniculate body lesions suffered a severe impairement. The inferior accessory optic tracts of the rat therefore, mediate the effects of excessive illumination on drinking. The visual pathways underlying endocrine responsiveness to continous illumination seem to be separable from those underlying visually guided behaviour.

Third Session : Metabolic and Humoral Factors

Bouman and colleagues (Groningen, Netherlands) reported that the level of circulating insulin got elevated within 48 hours after the VMH lesions. The plasma insulin response to an *i.v.* injection of HB 419 increased to twice that of sham-operated controls, and the pancreatic islet volume doubled while the insulin content of pancreas showed a decrease. Administration of alloxan (subdiabetogenic dose) in these hyperphagic rats, led to decrease of hyperphagia, reduction of gain in body weight, and impairment of islet function as tested with HB 419 and glucose injections. Since hyper insulinism in VMH lesioned rats which were pair-fed with sham operated animals on a 2 hour/day fixed amount food schedule was less marked than in rats on ad-lib schedule, it is possible that some pancreatic stimulation is also secondary to increased food intake. In any case hyperinsulinism seems to play an important role in maintaining hypothalamic hyperphagia. Louis-Sylvestre (College de France, Paris) measured the glucose uptake in 15 hr fasted Wistar female rats with and without lesions in the VMH nuclei and observed that VMH lesioned rats did not change the rate of glucose uptake from blood if there was no prior feeding. If however there was a prior intake of glucose

orally or by stomach infusion, a significant increase in the rate of glucose uptake occured. Such a high glucose uptake could be due to a change in the beta cell responsiveness which may be the primary cause of hyperphagia. This report falls in line with the studies in which VMH lesioned rats which were deprived of food, did not exhibit hyperinsulinism. Strubb and Steffens (Netherlands) followed the 24 hr feeding behaviour of rats and reported that they eat only a small amount during day time leading to an increase both in glucose and insulin plasma levels. During the early phase of night, however, they take big meals and produce a marked rise in plasma glucose level but not in the insulin level. The hypothalamic hyperphagic rats or those in which eating is induced on electrical stimulation of the hypothalamus, in contrast markedly increase their plasma insulin level during the night time. These findings are compatible with the view that insulin, as a determinant of glucose availability is directly involved in the control of feeding behaviour.

Le Magnen (College de France, Paris) measured O_2 consumption and CO_2 output alongwith plasma free fatty acids (PFFA) and insulin in rats under different feeding schedules along the 24 hr day-night cycle and reported that the day-night cycles of PFFA and plasma insulin ran parallel to the RQ cycle signifying the nightly synthesis and day-time mobilization of fats. Glucose uptake from blood of 4 hr food deprived rats was significantly faster in night than in day time. It seemed that the nighly eating and fat storage permitted the day time fat mobilization and therefore, the low intake of food. This negative correlation between night and day time food intake was absent in the hypothalamic hyperphagic animals. Le Magnen considers that a lipostatic mechanism controls a dark-light synchronized fluctuation of body fats in a narrow range around a "set-point". Such an influence on the control of feeding may be an indirect one in which the lipostatic cycle brings about an alternation of removal and supply of calories available for cell oxidation. Hustvedt and Lovo (Oslo, Norway) studied lipid metabolism by measuring the incorporation in vivo of a tracer dose of acetate 1-C^{14} in normal and VMH lesioned rats during some nutritional regimes. VMH lesioned animals incorporated more C^{14} than the control ones. This was interpreted as an increased acetate incorporation in fat depots because of the increased radioactivity found in the carcass fat of lesioned animals. The effect was the same whether lesioned animals were allowed to eat ad lib or were deprived of food signifying a rather fundamental derangement of normal fat metabolism.

Walike and Smith (University of Washington, U.S.A.) could not observe any evidence for the involvement of humoral factors affecting the central nervous regulatory mechanisms for feeding behaviour in their cross-circulation experiments in monkeys. However, they also noted that the feeding monkeys always had a higher post-absorptive glucose levels than the deprived monkeys by as much as 13-27 *mg*% inspite of a rapid and continuous cross-circulation extending over 3 days. Similarly, the glycerol levels of deprived monkeys remained higher than those of the feeding monkeys.

Booth (University of Sussex, England) reportad the inhibition of *ad*-lib feeding by the

modulation of gut signals through the post absorptive action of glucose and a number of metabolites of protein and fat metabolism. The intestinal chemo and osmoreceptors could be affecting food intake indirectly by causing a delay in the stomach emptying thus maintaining a longer lasting gastric distention. These effects were related to the caloric compensation required by the rats. Booth further demonstrated that moderate concentrations of glucose and aminoacids delivered parentrally also specifically suppressed feeding for several hours after their blood levels were returned to normal, indicating intracellular actions of these substances in the control mechanisms. Forbes and colleagues (University of Leeds, England) studied the metabolic regulation of food intake in sheep and found a significant increase in the ad-lib straw (3.5% crude protein) intake on intravenous infusion of methionine 1g/24 hr. Strangely enough, plasma methionine levels remained low throughout when measured before, during, and after the sheep ate diets of various protein contents.

Belbeck and Stevenson (University of Western Ontario, Canada) extended their earlier work and reported that the anorexigen isolated from the urine of fasted animals is a glycopeptide and is present in the plasma bound with alpha-2 globulin as demonstrated by immunoelectrophoresis. When the rats were limited to a 2 hr meal schedule, the level of their plasma anorexigen did show a progressive increase upto 6 hr after meals. An interesting experiment done by these authors was to decrease the food intake and thus produce cachexia in rats by infecting them with Walker 256 tumour cells. The plasma concentration of anorexigen increased as the tumours increased in size. Such an increase in the plasma concentration of the anorexigen which is coincident with the profound suppression of appetite, however, is of pathophysiological significance.

Mook (University of Virginia) reported the increase in food intake and weight gain when rats were ovariectomized. Estrogen injections in these animals decreased the food intake and and body weight. Adrenalectomy too reversed the effects of ovariectomy on food intake. Progesterone treatment induced weight gain. The progesterone effect was present in the ovariectomized and adrenalectomized animals. The sex hormones may be directly acting on the neural centres regulating food intake. Tarttelin and Gorsky (UCLA, School of Medicine) similarly observed significant depression of food and water intake, faecal and urinary output and body weight during oestrus in the rat. The pseudopregnant or ovariectomized rats in which cyclic changes of oestrogen secretion do not occur when given oestrogen treatment reduce their food intake and lose body weight. These studies corroborote the morphological evidence of the presence of oestrogen sensitive cells in the ventromedial hypothalamic areas.

Fourth Session : Role of Glucose

Oomura and colleagues (Kanazawa, Japan) reported their elegant electrophysiological studies demonstrating the effect of iontophoretic application of insulin and glucose on the discharge of lateral hypothalamic neurones. 16 out of 42 neurones decreased their activity when glucose was injected. 10 of the glucose responsive neurones increased their activity on

insulin injection. Oomura regards that the neurones inhibited by glucose are specifically sensitive to insulin. These findings are complementary to their earlier observations on the VMH neurones which increase their activity with glucose and decrease it with insulin. The mechanism by which *i.v.* insulin increases the food intake may be operating atleast partly through the direct effect of insulin on the VMH, and LH neurones. Nicolaides (College de France, Paris) reported the voracious feeding behaviour on 2 deoxy-D-glucose (2DG) infusion in rats. Vigorous eating was elicitable even in VMH lesioned rats. LH lesions in the perifornical region extending from preoptic areas to tuberal level, however, abolished this response. The voracious feeding response was concommittant with the decrease in oxygen consumption as elicited in the metabolic cages. Blass and Kraly (Johns Hopkins) found a significant depression of insulin or 2 DG induced eating when lateral preoptic areas were destroyed bilaterally. Houpt (University of Pennsylvania) failed to report any stimulation of food intake in 1, 2, 3 and 4 weeks old rats when 2DG was injected in various doses. The glucostatic controls of food intake therefore do not seem to be operative in suckling rats. She further demonstrated that the control of intake in suckling rats essentially occurs through the receptors indicating gastrointestinal filling.

Debon, Krimsky and From (New York State University) considered that hyperphagic response to gold-thioglucose is not dependent on the subjection of hypothalamic neurones to hyperinsulinaemia. In their alloxan-induced diabetic rats gold-thioglucose hyperphagia was still elicitable when they were administered 100 mg glucose 30 min prior to alloxan treatment. In these animals, the plasma insulin levels remained low and negligible throughout. Holub (Czechoslovakia) reported the existence of a relation between the blood glucose concentration and food intake in early weaned piglets. Miselis (University of Pennsylvania) reported the studies in which intraventricular infusion of 2 DG (7-14 μl, 3.0 molar) increased the food intake. Equal amounts of urea and 3 MG (3-0-methylglucose) infusion had no effect. Hypothalamic hyperphagic rats too showed the increased food intake on 2-DG infusion. Procaine injection in the VMH also increased food intake. 2-DG induced feeding, seemingly, can operate purely on the central neuronal basis without involving peripheral mechanisms and VMH is not necessary for 2-DG responsiveness. Novin (U.C.L.A.) reported similar studies and concluded that for the 2-DG action only the lateral hypothalamic area needs to remain intact.

Nijima (Niigata, Japan) showed a build up in the activity of efferent nerves to pancreas (vagal) and to the adrenals (splanchnics) when 2-DG or insulin was injected into the carotid artery of rabbits. Intracarotid glucose inhibited the activity of these nerves. These findings suggest the presence of a servo-control loop connecting blood sugar levels, the central nervous system, the efferent nerve fibres and secretory cells in adrenal medulla and pancreas which may be employed for the regulated control of food intake. Russek (Mexico) reported the extension of his work on hepatic glucoreceptors and demonstrated the production of anorexia (or aphagia) on partial or total deafferentation of liver. Russek also projected his film in which the

intraportal infusion of glucose and ammonia solution in dogs produced an aversion to food, and anorexia. Takahashi and Shriraishi (Tokyo, Japan) reported that lateral hypothalamic glucosensitive cells also induce increased gastric acid secretion to low blood glucose levels. This action is mediated through the vagus nerve.

Anand (New Delhi, India) gave an exposition of his concepts about the regulatory mechanism of food intake and the place of hypothalamic gluco-sensitive neurones in this regulation. Quoting from his earlier work and more recent electrophysiological studies done with anorexogenic drugs, he marshalled an impressive array of data supporting the presence of glucoreceptors sensitive to areteriovenous glucose differences.

Fifth Session : Regulation of Body Water

Almli (Ohio University) provided much useful data about the developmental aspects of water regulation and the onset of drinking behaviour in the rat which suggested that although the absolute levels of ad lib osmolality increase from birth to maturity, the threshold increase in osmolality required for the onset of drinking remains quite constant. Kozlowski and Sobocinska (Polish Academy of Sciences) found that the decrease of blood volume (8-32% of initial level) decreased the threshold of drinking in response to osmotic stimuli, which was proportionate to the degree of hypovolemia, and expansion of blood volume by isosmotic dextran increased the threshould of drinking. These effects were mediated through the vagosympathaic trunk suggesting that the volume receptors in the heart innervated by the vagus nerve tonically fire impulses inhibiting the thirst mechanism. Oatley and Toates (University of Sussex, England) reported experiments to quantitate the effect of thirst on food intake of rats and concluded that the effect of a given level of thirst as induced by the injection of different grades of hypertonic saline was to subtract a fixed quantity of food from the amount that would otherwise have been eaten had there been no thirst, and that 1 ml of water was worth between 0.3—0.4 g of food in all conditions. Stricker (Pittsburgh) reported that hypovolemic rats drink plain water at rates less than when provided with isotonic saline suggesting that overdilution or overhydration will act as an inhibitory stimulus for drinking although the rats remain hypovolemic. Carr and Titchen (Universsty of Melbourne) reported the time relations of increase in salivary secretion and blood osmolality with the food intake of sheep. They also noted that *i.v.* infusions of hyperosmolal saline into the portal circulation led to a marked decrease of parotid salivary secretion, and were followed by drinking. These investigations suggested the possibility of peripheral osmoreceptor mechanisms contributing to the control of parotid sativary secretion during ingestion of food. The role of salivary secretion in the control of drinking and feeding was also evident from the studies of Mendelson, Zec and Chillag (Rutger University) who reported that desalivate rats drank more than controls when maintained on dry food but less than controls when deprived of water for some period.

Vincent and colleagues (Bordeaux, France, and UCLA, U.S.A.) studied the activity of single neurones in the hypothalamus of conscious monkey alongwith EEG monitoring and

visually observed behaviour. They reported the occurrence of two types of neurones responding to intracarotid hypertonic injections: (1) Non-specific osmosensitive neurones responding both to osmotic as well as other sensory arousal stimuli. Their activity though associated with behavioural arousal was not related to drinking. (2) Specific osmosensitive neurones responding only to intracarotid hypertonic injections. Sensory arousal stimuli did not affect their activity. Their activation was always accompanied by a drinking response. The non-specific neurones lay scattered in the antero-lateral hypothalamus, while the specific neurones were localisable mainly in the supraoptic nuclei and the adjoining areas. Three more studies dealing with the activity of single neurones were reported in this session. Edinger (Rockefeller University) recorded various patterns of neuronal discharge in the conscious rabbit's hypothalamus during drinking. Hatton and colleagues (Michigan, U.S.A.) recorded the activity of anaesthetized rat's hypothalamic neurones under different states of hydration; and Wayner (Syracuse University) showed that glucose sensitive and sodium sensitive neurones in the rat hypothalamus can also increase their discharge rate under the influence of ethyl alcohol when given intravenously. These studies suggested the pluripotential nature of hypothalamic neurones implicated in feeding and drinking.

Falk (Rutgers University) reported the water electrolyte changes following dialysis induced hyponatremia in rats. Jackson and Scott (Royal Free Hospital, London) provided useful data about the water intake and urine output of the domestic cat which will be handy for comparison in studies on the feline water and electrolyte metabolism. Johnson and colleagues (Unsversity of Illinois) produced data on water metabolism in long distance runners.

Sixth Session : Renin-Angiotensin System

Peck and Epstein (Philadelphia) reported that angiotensin-II when injected into the lateral preoptic area (100-300 pg) caused antidiuresis and elevation in urinary Na and K in hydrated rats with chronic nasopharyngeal intragastric tubes. Lesions in the median eminence abolished these effects suggesting the involvement of ADH in the angiotensin mediated antidiuresis. Although drinking was also elicitable on angiotensin injections (200-300 pg), but tho most sensitive points were more rostrally placed and extended into septal and accumbens nuclei. Fisher (Pittsburgh) reported that injection of carbachol, angiotensin or isoproternol HCl, into the lateral septal area significantly increased drinking. Atropine blocked the drinking induced by carbachol but not that induced by angiotensin or isoproternol. The isoproternol effects were essentially of peripheral origin because bigger responses were obtained on subcutaneous administration of the same dose. Barrlet and Peters (Lausanne) studied the interaction between peripheral and central thirst inducing stimuli and reported that hyperosmotic and hypovolemic thirst induced by intraperitoneal injections of hypertonic saline or polyethylene glycol could not be mediated exclusively by the hypothalamic cholinergic thirst mechanisms. Covian, Rodrigues and Gentil (Sao Paulo, Brazil) reported that while atropine blocked the drinking induced by carbachol injections in

septal areas, it had no effect on the drinking induced by angiotensin injection in the same area. Alpha and beta adrenergic agents too did not affect the angiotensin induced drinking

Fitzsimons and Setler (Cambridge, England) reported that the drinking induced by angiotensin injections in the preoptic area was markedly reduced by the prior application 6-OH-DOPA or haloperidol. Drinking induced by carbacbol was blocked by atropine but not by 6-OH-DOPA, nor by haloperidol. Johnson (University of Pennsylvania) too induced drinking in rats by the injection of angiotensin in the preoptic regions of rat, and reported the dose-response relationship and summation of peripheral and central effects.

Haefeli and Peters (Lausanne, Switzerland) reported differences in the relationship between thirst and hypovolemia when effected through the administration of renin, angiotensin II, norepinephrine, and i.p. polyethylene glycol and suggested that the induction of hypovolemia is not the only mechanism by which renin and angiotensin II can induce an urge to drink. These substances may be directly acting on the hypothalamic centres, in addition. Wier (Glasgow, U.K.) reported some beautiful data from his clinical studies on patients of renal disorders, and brought to attention the fact that thirst is a prominent symptom of patients with sodium depletion, acute haemorrhage, and acute and chronic renal failure. In chronic renal failure, plasma levels of renin, angiotensin II and aldosterone were markedly increased. Bilateral nephrectomy sharply decreased the plasma levels of these substances, reducing simultaneously the urge to drink. Although thirst and aberration of taste are common symptoms of early pregnancy, Wier could not find any significant relationship between renin, angiotensin, and symptoms of early pregnancy. Love and Chinn (Glasgow, U.K.) reported the decrease in plasma levels of renin, angiotensin, and aldosterone when obese persons were put on therapeutic starvation schedule. They feel, however, that their findings of increased levels of plasma renin and angiotensin in patients of anorexia nervosa were unreliable because of the aberrant personality of patients. "At least in one such case, the patient, her relatives and her family minister conspired to confuse the results of metabolic investigations". Leenen and deJong (Utrecht, Netherlands) reported the plasma renin, water intake and urine output relationship in different grades of experimentally produced hypertension in rats. Rise of plasma renin activity corresponded with the increase of daily water intake and that of urine output. However, if animals were allowed to drink on a restricted schedule of 1 hr for 5 days and ad lib during the weekend, they did not develop the same high level of plasma renin nor of blood pressure as they would if put on ad lib schedule throughout the week. Changes in water metabolism, therefore, affect the development of renal hypertension.

Seventh Session : Long Term Regulation

Andik and Schmidt (Pecs, Hungary) reported that the decrease in calorie intake and body weight of rats on law protein diet was more when the diet diluent was glucose than when it was starch. Replacement of starch with glucose in diets which were not protein deficient had no effect on body weight or calorie intake. It seems that the intake of carbo-

hydrates is influenced by the amount of protein in diet. Cruce and colleagues (Rockefell University, New York) compared the feeding patterns of hypothalamic hyperphagic rats wit the genetically obese "Zucker" rats. These latter animals could put in more work for thei food than the VM lesioned hyperphagics. Suppression of food intake due to its dilution wit aversive taste was more in the VM lesioned hyperphagic than the Zuckers. Further, th Zuckers had an increase both in the size and number of their fat cells, but the VM lesione obese animals increased only the size of their fat cells. Widdowson (Cambridge, U.K. reported that more milk the new born rats gets, faster it grows signifying that the newbor rat is very immature compared with the newborn of many other species, and that it is no able to regulate its food intake till it is about 14 days old. The newborn pigs, guinea pigs and rabbits on the other hand have regulatory mechanisms which seem to be dependent on their respective body weights. Hamilton (V.A.H., Philadelphia) reported that if the monkeys (macaca mulatta) are permitted to become obese after hypothalamic lesions, 90% of them also become diabetic with typical symptoms of hyperglycaemia and glycosuria, Before these symptoms occur there is almost 10 fold inerease in the circulating levels of the plasma immunoreactive insulin in the presence of normoglycaemia. Hypothalamic hyperphagia, therefore, strongly resembles the disease entity called prediabetes in which the individuals have more than normal daily consumption of food without yet being hyperglycaemic. Pitts (Virginia University) reported the effects of force feeding and exercise on the regulation of food and exercise. Stellar and Spiegel (Pennsylvania University) reported that the short term regulation of food intake in human beings was not dependent on the regulation of caloric intake. In the long term experiments in which the subjects were required to ingest their meals without seeing how much they were eating, when the diet was diluted, 80% of the subjects were able to compensate for the caloric dilution by increasing their meal frequency and meal size. The subjects who failed to regulate caloric intake lost weight and reported increased hunger. Weihe (Zurich, Switzerland) reported that food intake of small animals is negatively correlated with ambient temperature and that the relationship is so precise that it can be used to determine the effect of changes in thermal environment on the animal's metabolism. Bines (Reading, U.K.) studied the regulation of food intake in thin and fat cows and reported that the thin cows eat more hay and concentrates than the fat cows. This seemed to be related to higher plasma and rumen concentrations of acetates in the fat cows presumably due to slower rate of metabolism of the acetates in these animals. Cioffi and Speranza (Naples, Italy) proposed a classification of different types of obesities which took into account various psychophysiological factors involved in the long term regulation of food intake. De Haan (Virginia) produced further evidence to support the thermostatic theory for the regulation of food intake. by studying the effect of various diets on the food intake of rats after starvation. Herberg (Queen Square, London, U.K.) demonstrated that certain behaviours like hoarding behaviour in the laboratory rats are dependent only on the long term needs of the animal and are apparently not inhibited by the postconsummatory processes signifying short term satiation. Hervey and Hervey (Leeds, U.K.) reported their

studies on the effect of various types of steroids on energy balance and discussed the possibility of the involvement of estrogens, progesterons and androgens in the long term central regulation of food intake. Lemonnier (Paris) studied a large number of metabolic end points in mice and rats after putting them on high fat diet schedules and reported that the obesity produced by high fat diet does not accompany hyperinsulinism and that the high amounts of fat in diet lead to a specially marked gain in weight of the genetically obese rats and mice.

Eighth and Ninth Sessions : The Central Nervous Controls

McKenzie and Denton (University of Melbourne) stimulated the diencephalon in the female sheep with permanent parotid fistula and were able to locate points which specifically led to increased salt intake. There was a good deal of overlapping between this and the so called "drinking area". Judging from the variability of reponse patterns and the rather wide areas from which motor responses like chewing, licking and swallowing, and the accompanying generalized agitation were obtained, it seems that electrical stimulation of different hypothalamic regions does not bear a simple determinant relation to the intake mechanisms, whether of food, water or salt. This point was brought home by Manchanda (New Delhi, India) who recorded the activities of various components of motor apparatus employed for ingestion by electrophysiological techniques and reported a number of response patterns on hypothalamic stimulation. These responses which had a common denominator in the rhythmic jaw and tongue movements interspersed with characteristic placement of swallows and salivation included pure feeding behaviour, rageful biting, and flight or running reaction, and were elicitable from throughout the length of far lateral hypothalamic regions extending from the lateral preoptic area to the posterior limit of mammillary bodies. More medial hypothalamic regions gave responses which resembled licking, lapping, vocalization and retching. Manchanda also reported that bilateral lesions in the classical "feeding" centres did not affect the motor capability of the ingestive apparatus because the pure feeding behaviour could still be elicited on electrical stimulation of the more anterior lateral preoptic areas. These lesions however did produce a sensory loss, because after the lesions the threshold for evoking reflex deglutition by the application of water at the back of tongue or by the excitation of superior laryngeal nerve was markedly increased. The lesioned animals, in addition showed a significantly increased EEG synchronization. Marshall and colleagues (University of Pennsylvania) reported a deficit of orientation to visual, olfactory, whisker touch and somatosensory stimuli after the lateral hypothalamic lesions. It is interesting to speculate that a generalized sensory neglect to orientational stimuli, combined with the increase in theshold of sensory stimuli necessary to initiate feeding reflexes per se, may really be the cause of lateral hypothalamic aphagia. An interesting report in this session was from Mogenson and colleagues (Western Ontario, Canada) who reported that high frequency stimulation in the zona incerta and perifornical areas in the rat led to feeding but low frequency stimulation at the same points produced drinking. These results are

consistent with the hypothesis that neural systems for drinking and feeding overlap eac other in the hypothalamus and limbic system and are activated differentially by low an high frequeney of stimulation respectively.

Rolls and Rolls (Oxford, U.K.) reported electrophysiological evidence for th involvement of amygdalo-hypothalamic pathway for the ingestive behaviour and confirme that lesions in lateral amygdala and pyriform cortex in general led to an increase in wate intake, and altered the day-night intake patterns and taste preferences. Fonberg (Warsaw Poland) reported increase in food intake on lateral amygdalar lesions and decrease in foo intake or aphagia of varying durations after lesions in the dorsomedial amygdala in dog These results indicated that the excitatory and inhibitory alimentary functions have doubl representation: in the hypothalamus and in the amygdala. Fonberg supported her thes by projecting a cine-film illustrating her observations in conscious dogs. Cytawa an Szponar (Lublin, Poland) reported that the heightened emotional reactivity in rats produce by lesions in the septal forebrain is accompanied by a marked increase in protein catabolism due to which these animals gain less weight than the controls, in spite of comparable amount of intake. Carey (V.A.H., Syracuse) reported that VMH and septal ablations had comparabl effects on emotionality, but only VMH lesions affected food intake regulation. Freedma and Andrew (Queen's University, Canada) reported that the cessation of glucose drinking whic is brought about by a functional decortication using the technique of 'spreading depression (SD) is related in its time course to the SD generated hyperglycemia.

Panksepp (University of Sussex, U.K.) disfavoured the concept of regarding VMH as purely inhibitory system mediating postconsummatory satiety, and quoted evidence for th hypothesis that VMH elaborates both excitatory and inhibitory control of feeding. Keese and Boyle (Wisconsin, U.S.A.) reported that prelesion starvation in rats reduced o completely eliminated the normal postlesion periods of hypothalamic aphagia and anorex and showed evidence that animals with lateral hypothalamic lesions can regulate their bod weight adjusted at a reference point set at a level lower than normal. Powley (Ya University, U.S.A.) also subscribed to the idea that damage to lateral hypothalamus cause the animal to undereat so as to regulate his body weight at a lower "set-point" an reported in addition that the body weight loss following LH lesions is due almost entirely t a reduction of fat stores. The "set-points", therefore seem to operate only with relation t the adipose tissue stores. All these studies are consistent with Panksepp's concep that VMH is well equipped with integrative substratum both for hunger an satiety signals, and that lateral hypothalamus merely modulates the integrative functio of VMH.

In sharp contrast to above were the studies which employed delicate knife cuts t disconnect the VMN from its surrounding structures and supported its inhibitory role McHugh, Gibbs and Bourne (New York) reported that parasagittal knife cuts lateral to th VMN in monkeys led to a marked increase in food intake thus establishing that inhibitor

signals from VMH travel lateralwards to the hypothalamic feeding centres. These animals, however still reduced their food intake when restrained in primate chairs, exposed to constant loud noise and given food adulterated with quinine indicating that inhibitory inputs can come to lateral hypothalamus from pathways other than those emanating from the VMN. Gold (State University, New York) using similar techniques in the rat reported that parasagittal cuts which were just lateral to VMN as well as those which were caudal and rostral to it increased the food intake. His conclusions were similar to those of McHugh and colleagues, and suggested that VMN projects to lateral hypothalamus through numerous indirect routes. These inhibitory pathyways according to his studies decussate in the supramammillary commissures, between the mammillary bodies, and in the midbrain and possibly also in the thalamus. Sclafani (Brooklyn, New York) however reported that the transection lateral to the VMN which is necessary to produce hyperphagia is usually quite a large one and extends into the anterior hypothalamus. Sclafani also compared the effects of these transections with the VMN lesion effects and observed that VMN lesioned rats suffer much more from emotionality disturbances than the transection animals.

Hoebel (Princeton University, U.S.A) reported that lateral hypothalamic outputs involved in feeding as measured by intake studies, and reward or aversion as measured by intracranial self stimulation were controlled by mutually linked or identical mechanisms, because treatment of animals with appetite depressant agents (propadrine or intragastric feeding) diminished the index of reward and increased that of aversion. Procedures which increased the appetite had the reverse effect on reward and aversion. Balgura and Davenport (Chicago, U.S.A.) felt however, that the recovered lateral hypothalamic-lesioned rats have a heightened motivation for food when compared with the normal controls, VM-lesioned hyperphagics or septal-lesioned rats! Spector (Universite Claude Bernard, Paris) disfavoured the idea of equalizing the intracranial self-stimulation (ICSS) indices with the reward or motivational system. He proposed that the 'ICSS' can be regarded as a complex reflex in the most extended sense of word, and that a self stimulated animal is essentially locked in a streotyped behaviour pattern which is continually generated by a non-physiological positive feed-back mechanism.

Tenth Session : Neuropharmacology of Ingestive Behaviour

Leibowitz (Rockfeller University, New York) provided evidence for the antagonistic functioning of alpha and beta adrenergic system in the hypothalamus. Alpha receptors which stimulated food intake and inhibited water intake were localized mostly in the ventromedial areas. Beta receptors which suppressed the food intake and stimulated the water intake were concentrated in the lateral hypothalamic areas. Injections of tranylcypromine which is a MAO inhibitor, in the VMN increased food intake, and in the LH, decreased food intake. According to Leibowitz, beta receptor stimulation produces satiation by inhibiting the lateral hypothalamic 'feeding centres' and alpha receptor stimulation produces hunger by inhibiting the VMN cells. Lehr and Goldman (New York Medical College, U.S.A.) claimed that they were the earliest to

report the appetite depressing effects of beta receptor excitation (Lehr, Mallow, Krukowski an Colon : Fed. Proc. 25 : 634, 1966). They further reported that thirst inducing and appeti depressing effect of serotonin was like that of a beta receptor for it could be blocked b propranolol. They conceded however that these effects of peripherally injected serotonin isoproternol and amphetamine may involve some possible role of a renal dipsogen like angio tensin. Meyer, Peskar and Hertting (University of Vienna, Austria) reported that not only bet agonists like isoproternol, nylidrine and isoxsuprine, but also hydralazines, and alpha recepto blockers like phentolamine and phenoxybenzamine elicited copious drinking, and significantl increased plasma renin activity when injected subcutaneously. Effects on both parameter were abolished by beta blockade. These studies support the hypothesis that drug induce effects on food and water intake are essentially mediated by the renin-angiotensi system.

Terpstra and Slanger (Utrecht, Netherlands) reported that application of graded dose of carbachol on the diagonal band of Broca caused graded amounts of drinking in the rat. The effects were blocked by central application of atropine and methyl-atropine. Drinkin induced by water deprivation or salt injection (15% NaCl) was not blocked by peripheral or central administration of atropine or methyl-atropine indicating that neural circuitry activated by water deprivation or hypertonicity is non-cholinergic. Khavari (University of Wisconsin, U.S.A.) providod evidence for the interactions between central and peripheral cholinergic mechanisms in the regulation of body fluid balance. Singer (Macquarie University, Australia). on the other hand provided data exhibiting interactions between cholinergic and adrenergic mechanisms both at central and peripheral levels. Grunden and colleagues (S.K.F. Labs, Pennsylvania) tested a number of pharmacologically active substances. Intrahypothalamic infusion of neuronal excitants like pentylenetetrazol and strychnine decreased food intake in fasted rats. Non-specific neuronal inhibitors like procaine and pentobarbital increased food intake in sated rats. Norepinephrine too elicited feeding but isoproternol had no effect. These effects were reported, presumably to be due to change in activity of the VMH. Histological confirmation of injection sites, however is still awaited. Search for chemical mediator in the CNS mechanisms controlling food and water intake also led to the intrahypothalamic injections or prostaglandins (PGE_1), 1 μl of 1 mg/100 ml of which when applied in VMH, LH, anterior commissure and perifornical areas depressed food and water intake in rats. This work was reported by Baile (also from S.K.F.). Prostaglandins are distinctively involved in fat metabolism. Possiblity of their direct CNS action in regulating the depot fat, and body weight is worth considering.

An excellent report of this session came from Ungerstedt (Karolinska Institute. Sweden) who successfully used the technique of intrahypothalamic injections of 6-OH-DOPA (6 hydroxydopamine) to selectively interrupt the nigro-striatal dopamine pathways coursing through the lateral hypothalamus, and produced the classical type of aphagia and adipsia. Degeneration of dopaminergic nerves to corpus striatum seem to be enough to produce serious

aphagia and adipsia. Injection sites which produced these effects were localized in lateral hypothalamus, substantia nigra and ventral tegmental area. All these sites have also been shown to produce rhythmic jaw movements and swallowing on electrical stimulation (Manchanda, 1965, Ph.D. Thesis). Evetts, Fitzsimons, and Setler (Cambridge University, U.K.) reported that 6-OH-DOPA injections (8 μg) in preoptic areas caused depletion of noradrenaline in the septum, hypothalamus and preoptic areas, but not in the corpus striatum. 6-OH-DOPA injected rats started eating after a latency of about 1 hr. This was claimed to be due to the release of noradrenaline for the time course of initiation of eating ran parallel to that of norepinephrine depletion and because the eating response was abolished by a prior administration of adrenegic blocking agents. Smith and Stromayer (Cornell, New York) also reported that injections of a total dose of 115—230 μg of 6-OH-DOPA in the lateral hypothalamus produced aphagia and adipsia in the rat. The adipsic rats did not drink even when challenged with hypertonic saline or polyethylene glycol. These reports can be interpreted as evidence for a significant involvement of the catacholamine neurones of the hypothalamus in the control of feeding as well as drinking behaviour.