11 Mechanisms by Which Drugs and Hormones Activate and Block Release of Pituitary Gonadotropins. C. H. SAWYER (U.S.A.).

Results of stimulation, lesion and transplantation experiments reveal that the release of pituitary gonadotropins is controlled by the nervous system in both reflexly and spontaneously ovulating animals. Localized electrical stimulation studies have indicated that certain parts of the hypothalamus and rhinencephalon are directly involved. Such drugs as picrotoxin, intraventricular histamine (under weak pentobarbital anaesthesia), copper acetate and intraventricular nor-epinephrine in pituitary-activating dosages stimulate characteristic electroencephalographic (EEG) changes in rhinencephalic pathways, and their influence on the pituitary gland is blocked by basal hypothalamic lesions. Low frequency (5 c/s) electrical stimulation of hypothalamic and rhinencephalic areas evokes a characteristic "EEG after-reaction". Drugs such as atropine, dibenamine and pentobarbital, which block the release of pituitary ovulating hormone, markedly elevate the EEG after-reaction threshold in dosages which do not necessarily elevate the threshold of EEG arousal (evoked by high frequency, 300 c/s, stimulation of the reticular formation). Sex steroids which at first facilitate and later inhibit release of pituitary gonadotropins have temporarily appropriate biphasic effects on the EEG after-reaction threshold whereas steroids which merely block the pituitary only elevate the after-reaction threshold. Antifertility progestogens such as nor-ethynodrel also have a rather specific effect on this threshold. The receptor site of steroid activity would appear to be in the basal hypothalamus as evidenced by ovarian and testicular atrophy following implantation of oestradiol and testosterone, respectively, into the hypothalamus but not following their implantation into other sites in the brain or hypophysis.

12 The Location of Renin in the Rabbit Kidney. W. F. COOK and G. W. PICKERING (United Kingdom).

It is not yet exactly known which cells produce renin but the evidence suggests that they occur near the glomeruli. Cook and Pickering (1959) have shown that glomeruli, separated magnetically from rabbit cortex contains a much higher concentration of renin than the remaining non-glomerular tissue. Glomeruli with capsule and attached fragments of closely adjacent tissue contained more renin per mg of nitrogen than glomeruli without these attachments. Glomeruli with attachments can be selected and cut into two halves, one including the vascular pole region and the other not. In this way Cook showed that renin is confined to the vascular pole half of the glomeruli. In this region occur three histologically distinct cell groups, one of which, the juxtaglomerular cells, contain cytoplasmic granules. Others have found that the number of granules in these cells and the renin content of the kidney show parallel changes in several different experimental situations. In view of this it seemed of interest to see whether renin occurred in association with subcellular particles. Rabbit kidney cortex homogenates were first fractionated by differential centrifugation in 0·3 M sucrose. The renin was confined to the "large granule fraction" which was further fractionated on sucrose density gradients. Preliminary experiments show that renin is associated with particles which can be separated from mitochondria. These particles are readily disrupted by mechanical agitation and osmotic shock, whereupon renin is released into solution.

13 The Basophil Response: A New Area in Cytopharmacology. L. JUHLIN and W. B. SHELLEY (U.S.A.).

The chemistry of the circulating basophilic granulocyte (basophil) gives clue to its significant role in the body economy. However, this cell has largely eluded direct observation since it is rare and fragile. Cell counts have been relatively unsatisfactory since they do not regularly reflect the functional activity of the basophil. Recently, we have developed a cytologic technique for observing the morphologic changes in the basophil as it responds to a variety of stimuli. The method consists of rapid cell fixation followed by concentration and selective staining with toluidine blue. The basophils are then classified morphologically (basophil differential) on the basis of the degree of degranulation. The method permits study of the effect of drugs both *in vivo* and *in vitro*.

Results will be presented on the basophil response in man to steroids, histamine liberators, and other pharmacodynamic agents. Particular data will be given on the detection of urticarial and anaphylactoid reactions to drugs.

14 Action of Antihistamine Drugs on Ion and Water Movements in Vitro. K. AHMED and J. D. JUDAH (U.S.A.).

Antihistamine drugs have been shown to inhibit water and ion movements in a number of cells and subcellular structures. Mitochondrial swelling is greatly inhibited by these compounds at concentrations at which no effect is seen on respiration or phosphorylation. Mitochondrial contraction is similarly inhibited at the same concentrations. Identical results have been obtained with other systems, e.g. mammalian red cells in which K uptake is inhibited by antihistamines at concentrations which also reduced the rate of osmotic hemolysis. The K uptake of rat liver slices and of Ehrlich ascites tumour cells is also greatly reduced by these drugs.

The mechanism of action of such compounds has been investigated and it is found that phosphoprotein phosphorus turnover is apparently closely