(3) The splitting of the high-energy phosphate bond of the phosphorylated compound requires Na^+ in the medium and is highly increased by adding K^+ when the medium contains Na^+, while K^+ alone has practically no effect.

(4) G-strophanthin which specifically inhibits the active linked transport of Na^+ and K^+ in the intact cell also inhibits the $Na^+ + K^+$ activated splitting of the high-energy bond of the phosphorylated compound.

(5) There is indirect evidence that the particle studied is derived from the surface membrane of the intact cell.

(6) A particle which contains a system which has the same specificities for Na^+ and K^+ has also been isolated from other tissues where there is an active linked transport of Na^+ and K^+, namely from brain, kidney and heart muscle.

The relationship of the particulate system to the active linked transport of Na^+ and K^+ across the cell membrane will be discussed.

6 Pharmacological Control of Release of Hormones Including Antidiabetic Drugs. Introductory Remarks. R. COURRIER (France).

7 Pharmacological Actions of the Hypoglycaemic Arylsulphonamides upon the Histophysiology and the Physiology of the Beta-cells of the Islets of Langherhans of the Pancreas. A. LOUBATIERES (France).

The hypoglycaemic arylsulphonamides (thiodiazole or urea derivatives) have a preferential tropism for the pancreas (pancreatotropism) and especially for the beta-cells of the islets of Langerhans (betacytotropism). The betacytotropism is mainly shown by the degranulation of the beta-cells and by other histological modifications demonstrated with electron microscopy.

Hypoglycaemic sulphonamides are betacytotrophic. They produce a hyperplasia of the islets and stimulate the formation of new insulin secretory beta-cells. There follows an increase in the total amount of the beta-cells and an increased capacity of the endocrine pancreas in blood glucose regulation.

We have at the present time strong evidence showing that hypoglycaemic sulphonamides are insulin-secretory stimulating substances. The venous blood coming from the pancreas is more hypoglycaemically active after administration of these drugs that it was before: its "plasma insulin activity" as well as its endogenous insulin content increases. This is the main reason why these drugs are strongly effective in the treatment of human diabetes characterized by sluggishness or relative depression of insulin-secretory process.

The arylsulphonamides manifest an antidiabetic action against meta-alloxanic, meta-hypophyseal or spontaneous diabetes of moderate intensities. They counteract the establishment of idio-hypophyseal diabetes in a dog. They exert a preventive action against the exhaustive process which occurs "spontaneously" in the beta-cells of the pancreas remnant of a subtotally depancreatized animal. These phenomena are in direct connexion with the actions (stimulation, neoformation, regeneration) exerted by these sulphonamides upon the apparatus of the beta-cells. Clinical trials plead for the possibility of the use of these drugs as prophylactic agents against the development of full diabetes in human beings predisposed to this illness.

8 Experimental Investigations with Sulphonureas (S.U.). A. BÄNDER (Germany).

The effects of oral hypoglycaemic compounds upon the enzyme-system, the liver and the peripheral carbohydrate metabolism do not sufficiently explain the hypoglycaemic action. Experimental animals and patients deprived of the pancreas do not exhibit any hypoglycaemic reaction, provided that the gland is removed, for several days.

There is agreement that the main action is to be found in releasing insulin from the pancreas. How this liberation is effected constitutes a question of paramount interest.

According to results by Wrenshall *et al.*, a large number of the diabetics who develop the disease when adults have a sufficient amount of insulin in the gland, sometimes even more than non-diabetics. There remains the question why these patients are diabetics. Some evidence has been obtained that in these patients there is an abnormal binding of insulin in the pancreas. Thus, the difference in blood sugar curves between non-diabetics and diabetics could be explained.

Experiments of Aiman *et al.* showed that plasma-bound insulin could be released by S.U.

Our own investigations have demonstrated *in vitro* a degranulation of isolated β-cells under the influence of S.U.

Reviewing these observations one may assume that S.U. are exerting their effects by means of physico-chemical properties. It is suggested that these qualities produce a removal of this abnormal binding; in this way adequate amounts of insulin are released.

9 Pharmacological Effects of Some Chemical Compounds of Biosynthesis and Secretion of Thyroid Hormones. R. MICHEL (France).

The main steps in the biosynthesis and secretion of thyroid hormones are: iodide concentration, iodotyrosines formation, iodotyrosines coupling, thyroglobulin proteolysis, enzymatic deiodination of iodotyrosines followed by iodothyronines secretion.

Various chemical compounds modify thyroidal iodine metabolism. Thiocyanate, perchlorate and other isoelectric anions of about the same volume inhibit iodide concentration. They act competitively with I^- which probably fits into some specific

sites of oxidase. Thiouracil derivatives not only block iodination but also depress the formation of thyroxine from diiodotyrosine *in vivo* ann *in vitro*. Drugs of this type interfere in some way with thyroxinogenesis and a new iodoprotein appears after a long treatment with propylthiouracil. The relative potency of antithyroid drugs was established by *in vivo* and *in vitro* methods. Relation between chemical structure and antithyroid action was studied. Derivatives of thiourea, mercaptoglyoxaline, thioglyoxalone and mercaptotriazole possess antithyroid properties. The mode of action of these drugs seems to be related to a blockade of oxidizing enzymes involved in organification of iodine. Reducing agents stimulate cathepsins and accelerate the rate of liberation of hormones; thyroxine inhibits deiodination of iodotyrosines preventing uptake of thyroidal iodide.

As iodine metabolism depends of TSH secretion, any compound acting directly or indirectly on the stimulation of TSH produces as effect on hormonogenesis. That is the case for thyroxine, 3:5:3′-triiodothyronine and also for the non-calorigenic 3:3′:5′-triiodothyronine which are concentrated by the pituitary and block TSH secretion. Adrenaline decreases ^{131}I uptake and produces thyroid hyperplasia.

Compounds such as 3:5-diiodo-4-hydroxybenzoylbutylester affect the rate of metabolism of iodohormones; the resulting changes in PBI level modify TSH secretion. Cortisone works by another way, it exaggerates excretion of iodide by kidneys; circulating iodide is reduced and then ^{131}I thyroid uptake decreases.

Thus many chemical products active on peripheral iodine metabolism interfere with biosynthesis and release of thyroid hormones.

10a Action de Quelques Dérivés du 2-Aminomethyl-Benzodioxan sur l'Equilibre Hormonal du Cycle, de la Pseudo Grossesse et de la Grossesse chez la Ratte. F. Bovet-Nitti et G. Bignami (Italy).

Des recherches réalisées sur l'effet de différents dérivés sur la grossesse chez la ratte ont montré que le traitement au cours des premiers jours de la gestation peut provoquer des accidents dont les manifestations n'apparaissent parfois que d'une manière tardive.[1] Dans le cas d'un sympatholytique, le Piperoxan (933F.), l'on a observé que 100 mg/kg administrés par voie orale le jour 1 dé la grossesse empêchent l'ovoimplantation chez 30 à 50 pour cent des rattes sans provoquer d'anomalies chez les autres animaux du lot. L'étude de dérivés voisins montre que cette action ne parait pas liée aux propriétés sympatholyques des ces produits.

Une activité sur la gestation a été également reconnue à certains dérivés du benzodioxan à fonction hydrazine, inhibiteurs des monoamino oxydases (MAO). Dans le cas du N′-1:4-benzodioxan-2-méthyl-hydrazine (2596IS)[2] l'administration de 100 mg/kg par voie orale le jour 1 de la grossesse provoque chez 50 pour cent des rattes soit une inhibition partielle ou totale de l'implantation soit, exceptionnellement, la résorption précoce d'une partie des nidations.

Diverses considérations font penser que l'effet du Piperoxan et du 2596IS est d'prigina centrale et que ces substances sont susceptibles de modifier l'équilibre hormonal par l'intermédiaire des secretions de l'antéhypophyse. Il a été en effet remarqué[3] que le 2596IS s'oppose dans le 100 pour cent des cas à la pseudogrossesse provoquée par la Réserpine et dans une proportion pouvant aller jusqu'à 40 pour cent à celle dérivant d'une stimulation mécanique.

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1. Bovet-Nitti, F. and Bovet, D. (1959), *Proc. exp. Biol. Med.*, **100,** 555.
2. Bovet-Nitti, F., Orsingher, O., Land-Vittory, R. and Bovet, D. (1961), *Comptes Rendus Acta Scand.*, **252,** 614.
3. Bignami, G., *Rendiconti Ist. Sup. Sanitâ.* In press.

10b Action of Certain Derivatives of 2-Amino Methyl-Benzodioxan on the Hormonal Equilibrium of the Reproductive Cycle, Pseudopregnancy and Pregnancy in the Rat. F. Bovet-Nitti and G. Bignami (Italy).

Investigations on the effect of various derivatives on pregnancy in the rat have shown that treatment during the first days of the gestation period can cause accidents which sometimes only become apparent later.[1] In the case of the sympatholytic, Piperoxan (933F) it has been observed that 100 mg/kg administered orally on the first day of pregnancy prevent the implantation of the ovum in 30 to 50 per cent of the rats without causing any abnormalities in the other animals of the group. The study of related derivatives shows that this action does not appear to be related to the sympatholytic properties of these drugs.

Certain derivatives of benzodioxan with hydrazine properties, which inhibit monoamino oxydase (MAO), have also been found to affect gestation. In the case of N′-1:4-benzodioxan-2-methyl-hydrazine (2596IS) the administration of 100 mg/kg orally on the first day of pregnancy provokes either partial or total inhibition of implantation in 60 per cent of the rats or, in exceptional cases, the precocious absorption of the implant.

Various considerations lead to the hypothesis that the effect of Piperoxan and of 2596IS is of central origin and that these substances can modify the hormonal equilibrium through the intermediacy of the anterior hypophyseal secretions. It has, in fact, been observed[3] that 2596IS counteracts the pseudopregnancies due to Reserpine in 100 per cent of the cases and in up to 40 per cent in cases where it is due to mechanical stimulation.