the cause seems to be the uterine involution and the trauma of the delivery.

The low BKG content of the fetal blood at birth and in the first days of extrauterine life could reflect the immaturity of the liver in the newborn.

33. The Purification and Some Properties of Human Plasma Kallidinogen. JACK V. PIERCE and MARION E. WEBSTER (*Laboratory of Metabolism, and Laboratory of Cardiovascular Physiology, National Heart Institute, Bethesda, Md., U.S.A.*).

Kallidinogen, a plasma α_2-globulin which produces kallidin or bradykinin when treated with kallikrein, trypsin, or snake venom, has been purified about 400-fold over the starting human plasma and in 10% yield. This was accomplished by the following four steps: (1) DEAE-cellulose chromatography and (2) rechromatography, (3) hydroxylapatite chromatography, and (4) Sephadex G-200 gel filtration. Linear gradients of phosphate buffer were used in steps (2) and (3). Step (2) gave two peaks of activity in a ratio of 3·9. Step (3) on the combined activity from (2) also gave two peaks, I and II in the order of their elution, but in a ratio of 0·7. Gel filtration of peak I gave a major activity peak with a K_d of 0·46 and a minor peak with a K_d of about 0·23. Peak II on the same G-200 column gave only one activity peak (K_d = 0·45), from which the purest material was obtained. Hydroxylapatite chromatography of peak II material, with a linear gradient of phosphate buffer in the presence of 1 M sodium chloride, also gave two peaks of activity in a ratio of about 1·0. Experiments are being done to clarify this confusing situation. Studies of the physicochemical and biochemical properties of kallidinogen will be made as soon as material satisfying several criteria of homogeneity has been obtained.

34. Characterization of Kinins in Wasp Venom. J. L. PRADO,* Z. TAMURA,† E. FURANO, J. J. PISANO and S. UDENFRIEND (*Laboratory of Clinical Biochemistry, National Heart Institute, Bethesda, Md., U.S.A.*).

At least six kinin fractions were observed when wasp venom preparations (genus *Polistes*) were chromatographed on columns of carboxymethyl cellulose and carboxymethyl Sephadex. The first two kinins had pharmacological and chemical properties similar to bradykinin and kallidin respectively. However, when the fluorescent dimethylnaphthylsulfonyl (dansyl) derivatives were examined by thin-layer chromatography (TLC) several biologically active fluorescent bands were observed, none of which corresponded exactly to dansyl bradykinin or dansyl kallidin. The fluorescent peptide derivatives had 1–2% the potency of the free peptide in the estrous rat uterus assay. Most of the kinin activity of venom (>50%) was in fraction 3 which consisted of a single peptide as revealed by TLC of the dansyl derivative. It had the amino acid composition: Arg_2, Asp, Gly_2, Glu, Leu, Lys_2, Phe_2 Pro_3, Ser, Thr. Chymotrypsin but not trypsin destroyed biological activity. An active peptide was isolated from the tryptic digest. It was composed of Arg_2, Gly_2, Phe_2, Pro_3, Ser, with glycine the N-terminal amino acid. The peptide was indistinguishable in chemical and biological tests from synthetic glycylbradykinin, also termed gly^1-kallidin (Schröder and Hempel, *Experientia, Basel* **20**, 529, 1964). To be determined are the amino acid sequence of undigested fraction 3 and the structures of the kinins in the other fractions. (Reference peptides were kindly supplied by E. Nicolaides and E. Schröder.)

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35. Kallikrein in the Submaxillary Gland. M. SCHACHTER (*Dept. of Physiology, Univ. of Alberta, Edmonton, Alberta, Canada*).

Shortly after salivary kallikrein was described (Werle and Roden, 1936), it was suggested that this substance was the mediator of chorda-tympani-evoked vasodilatation in the submaxillary gland and tongue (Ungar and Parrot, 1936). This suggestion was made to explain the fact that vasodilatation in the gland caused by stimulation of the chorda-tympani nerve is not blocked by doses of atropine, which readily block the secretory response. Further work led to the specific conclusion that vasodilatation in the active gland is secondary to secretion; i.e. it is caused by kallikrein passing from the secretory cells into the tissue spaces where it releases the vasodilator peptide, kallidin (Hilton and Lewis, 1955, 1956, 1958).

Our experimental results listed below, however, have led us to conclude that vasodilatation produced in the submaxillary gland by stimulation of the chorda-lingual nerve is *not* mediated by kallikrein, but that true vasodilator nerve fibres, probably cholinergic, are present in this nerve.

In the cat. (a) The vasodilatation resulting from close arterial injection of dialysed cat saliva into the salivary gland with intact blood circulation differs from that caused by stimulation of the chorda-lingual nerve or by acetylcholine (ACh) similarly injected: it is slower in onset, it is not so great, and it is generally more prolonged. (b) Desensitization of the blood vessels to the vasodilator action of a standard dose of bradykinin

or to dialysed cat saliva injected close-arterially, leaves an equivalent vasodilatation caused by stimulation of the chorda-lingual nerve or by injection of ACh practically unaffected. (c) During prolonged perfusion of the gland with horse serum, from which cat saliva releases no kallidin, stimulation of the chorda-lingual nerve still produces marked vasodilatation, although intra-arterial injections of dialysed cat saliva are ineffective. (d) It is possible to deplete the submaxillary gland of kallikrein by ligation of the duct for 3 days and subsequent stimulation of the sympathetic nerve. Chorda-lingual nerve stimulation still produces a normal vasodilatation in such a kallikrein-depleted gland.

In the rabbit. The secretion and vasodilatation in the submaxillary gland produced by chorda-lingual nerve stimulation are reduced or blocked in parallel by atropine.

36. Recent Developments in the Chemistry of Gastrin. R. C. SHEPPARD (*The Robert Robinson Laboratories, Liverpool Univ., Liverpool, England*).

The natural hormone gastrin appears to play an important role in digestive processes, particularly in the control of gastric acid secretion. The recent isolation[1] of two gastrins from hog antral mucosa has been followed by their structural elucidation[2] and total synthesis.[3] Both hog gastrins are heptadecapeptide amides, and differ only in the sulphation of a tyrosyl residue in one hormone. Further synthetic work has enabled the minimal structural requirements for gastrin-like activity to be established, and has yielded a number of analogues with interesting biological properties.

1. R. A. GREGORY and H. J. TRACY, *Gut*, **5**, 103 (1964).
2. H. GREGORY *et al.*, *Nature* (*Lond.*) **204**, 931 (1965).
3. J. C. ANDERSON *et al.*, *ibid.*, p. 933.

37. Prevention of the Edematous Arterial Reaction and the Atherosclerosis of Cholesterol-Fed Rabbits by Anti-Bradykinin Agents. TAKIO SHIMAMOTO, FUJIO NUMANO, MASAYOSHI KUBOTA and TSUTOMU FUJITA (*Institute for Cardiovascular Diseases, Tokyo Medical and Dental Univ., Tokyo, Japan*).

Edematous arterial reaction (*Jap. Heart J.* **3**, 581, 1962) is an immediate and general effect in arterial walls of animals after such stresses as administration of atherogenic substances or traumatization. The reaction consists of a microscopic swelling of arterial wall, owing to the accumulation of serous material in the amorphous extracellular spaces of intimal and medial layers, which shows a close similarity to *das initiale fettfreie Ödem*, the hypothetical initial stage of human atherosclerosis of the German school.

In an attempt to prevent the reaction, ergotamine tartrate, atropin, pyribenzamine, Dexamethasone, etc. were without effect in relatively large doses, whereas the following substances were effective. (1) Trasylol (300 U/kg i.v.): a bradykinin-forming (polyvalent proteolytic) enzyme-inhibiting substance. (2) "Anti-bradykinin agents in veins"; acetylsalycilic acid (50 mg/kg p.o.), nialamide (50 mg/kg p.o.), cyproheptadine (5 mg/kg p.o.), and pyridinolcarbamate (1 mg/kg p.o.).

The atheromatous changes in cholesterol-fed rabbits were slightly inhibited by a nialamide (10 mg/kg/day p.o.) and cyproheptadine (5 mg/kg/day p.o.) and markedly inhibited by pyridinolcarbamate (5 mg/kg/day p.o.), showing a characteristic tendency to fibrous healing. Pyridinolcarbamate not only minimized very noticeably the atheromatous changes and accumulation of cholesterol in arterial walls ($P < 0.01$) but also prevented remarkably the formation of atheroma and its fatty degeneration and necrosis formation ($P < 0.01$) in animals kept on a cholesterol diet for 15 weeks, which had a high serum cholesterol level amounting to 1,735 ± 169 mg/kg during the last 5 weeks of experiment.

38. Some Physiological and Pathological Roles of Kininogen and Kinins. F. SICUTERI, G. FRANCHI, M. FRANCIULLACCI and P. L. DEL BIANCO (*Centro Cefalée, Clinica Medica dell'Università, Florence, Italy*).

The kininogen–kinin system was suggested to be of physiological importance in the control of microcirculation. According to our experiments, kininogen is higher in arterial than in venous blood.[1] The capillary bed exhibits a strong kinin releasing and clearing power.[2] Hydrolysis of kinins is higher in venous than in arterial blood.

Bradykinin and kallidin may also act as mediators in some experimental and vascular pains.

Evidence of strong sensitization to the pain-producing properties of bradykinin, kallidin, and kallikrein by 5-hydroxytryptamine on nociceptors has been shown in man. The importance of this potentiation in man during myocardial infarction and other thromboembolic accidents is emphasized.[3]

Experimental and laboratory findings support our hypothesis concerning the pathogenic importance of the presence of kinins in cerebrospinal fluid during subarachnoid hemorrhage. Kinins are released largely by dilution when blood is mixed with cerebrospinal fluid in subarachnoid spaces. Headache and meningeal syndrome of subarachnoid hemorrhage may be provoked by the pain-producing and inflammatory properties of kinins.[1]