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]

In some clinical and pharmacodynamic conditions, a decrease of kininogen level in plasma can be observed.

The general and circulatory picture during direct release of kinins by trypsin and kallikrein in man has been studied and compared with the clinical pharmacology of some hypotensive peptides such as synthetic bradykinin, kallidin, eledoisin, and physalaemin.[5, 6] The effects of some antifibrinolytic compounds such as Trasylol and ε-aminocaproic acid will be shown.

Some therapeutical trials with synthetic and natural peptides (plasma kinins) will be discussed.

1. F. SICUTERI, P. PERITI, G. FRANCHI and D. SANTINI, *Boll. Soc. ital. Biol. sper.* **39**, 310 (1963).
2. F. SICUTERI, P. PERITI, B. ANSELMI and M. FANCIULLACCI, *ibid.*, p. 314.
3. F. SICUTERI, M. FANCIULLACCI, G. FRANCHI and P. L. DEL BIANCO, *Life Sci.* **4**, 309 (1965).
4. F. SICUTERI, *Settim. med.* In press (1965).
5. F. SICUTERI, M. FANCIULLACCI, G. FRANCHI and S. MICHELACCI, *Experientia (Basel)* **19**, 44 (1963).
6. F. SICUTERI, M. FANCIULLACCI and P. L. DEL BIANCO, *Settim. med.* **52**, 1221 (1964).

39. Contribution to the Sedative Action of Substance P. P. STERN (*Dept. of Pharmacology, Medical Faculty, Univ. of Sarajevo, Yugoslavia*).

We have already indicated that substance P (SP) acts as a sedative. In these experiments fighting male mice (fighting induced by keeping mice isolated from each other for 21 days) became tranquil 15 to 30 minutes after the application of SP. This effect has been examined with SP of purity 6 U, 75 U, and 300 U/mg. Groups of mice received from these fractions 5,000 U/kg injected in 0·2 cc/g, i.p. Substance P destroyed with chymotrypsin had no effect on the control group. Tranquil mice became belligerent again if given 25 mg demethylimpiramin i.p. We take this as additional evidence for the central sedative action of substance P. Since in this test impure (6 U) and relatively pure (300 U) SP had the same effect, we believe that the test could be applied for example during the purification of SP. Substance P is a polypeptide that not only contracts the ileum of the guinea pig but has a sedative action as well. We have already shown that the other central effects of pure SP do not parallel the effect on intestine; for example, purified SP (270 U/mg) no longer has antistrychnine-like action. On the other hand, Krivoy has showed that very pure SP (10,000 U/mg) still retains neurotropic action.

40. The Search for Peptides with Specific Antibradykinin Activity. JOHN MORROW STEWART and D. W. WOOLLEY (*The Rockefeller Institute, New York, N.Y., U.S.A.*).

Structure–activity relationships in the bradykinin molecule were studied with the aid of over forty new analogs of bradykinin. These analogs (octa-, nona-, and decapeptides) were synthesized and tested on smooth muscles for bradykinin potency and for their ability to act as antagonists of bradykinin. The compounds were made by slight modifications of the Merrifield method of solid-phase peptide synthesis, and were obtained analytically pure. Single replacements of one amino acid residue by some other were ineffective for formation of antimetabolites, as were changes in the optical configuration of the amino acids. Greatest antibradykinin activity was found among analogs in which both phenylalanines had been replaced by O-methyl tyrosine. These analogs showed antibradykinin activity on rat uterus at low concentrations, while at much higher concentrations bradykinin-like action was observed. The antibradykinin activity fluctuated widely from animal to animal. Various structural alterations, especially in the serine position and in the carboxyl end, were explored in an attempt to obliterate the bradykinin-like action with retention of the antibradykinin effect. No compound has yet been found which showed high potency as an antagonist but had no bradykinin-like activity.

41. An Apparatus to Simplify the Bioassay of Vasoactive Substances. E. STÜRMER and H. WOHLFART (*Biological and Medical Research Division, Sandoz Ltd., Basle, Switzerland*).

An automatic apparatus has been constructed for assaying vasoactive substances by comparing their effect on the blood pressure with that of standard substances. Standard or test solutions are automatically injected by the intravenous route with the aid of two infusion pumps, operated intermittently. Dosage and sequence of the injections follow a prearranged program. The blood pressure changes in response to the injections are recorded by means of a strain gauge and transformed to impulses. The reaction maxima are printed out and the results are evaluated by computer.

This procedure saves manpower and time and makes for greater accuracy.

42. Purification and Some Enzymatic Properties of Bradykinin-Releasing and -Destroying Enzymes in Snake Venoms. TOMOJI SUZUKI, SADAAKI IWANAGA and TADASHI SATO (*Institute for Protein Research, Osaka Univ., Osaka, Japan*).

During purification of the bradykinin-releasing enzyme of the venom of *Agkistrodon halys blom-*