THE ROLE of the central nervous system in the pathogenesis of cardiovascular disease has been emphasized in the Russian literature.\(^1\) This concept is perhaps most pronounced in their research on arterial hypertension,\(^2\) but is applied also to coronary artery disease, and particularly to angina pectoris.\(^3\)\(^4\)

The large experimental and clinical material accumulated in the past decade by Russian authors cannot be reviewed in detail in this article. A few representative references, however, are given as general background for the main topic: the effect of reflexes from gastrointestinal receptors on coronary insufficiency. In prolonged experimental neurosis in monkeys, produced by conflicting conditioned reflexes, in some of the animals electrocardiographic changes developed that were identical to those of human left ventricular ischemia. Apparent angina attacks developed, and one monkey died of myocardial infarction, confirmed by autopsy.\(^5\)

Vovsi\(^6\) found pronounced changes of the electroencephalogram in 30 patients with coronary artery disease during attacks of angina pectoris, together with typical S-T depression in the electrocardiogram. Zamislova and Bodnar\(^7\) reported a higher incidence of disturbance in the electroencephalogram and other central nervous system functions in 58 patients with coronary heart disease than in healthy subjects. Gukasyan and Tapitser\(^8\) stressed the role of the central nervous system in the development of myocardial infarction on the basis of clinical impression. Since central nervous system effects on the heart have to be mediated through the autonomic nervous system, effects of stimulation of autonomic centers, vagal, sympathetic, and cardiac nerves on coronary circulation have been studied on a rather large scale. Ligature of one branch of the left coronary artery produces spasm in other branches, which can be abolished by bilateral vagosympathetic block.\(^9\)

After ligation of the anterior descending branch of the left coronary artery in dogs the majority of animals did not develop myocardial infarction, but vagal stimulation after ligature produced infarction.\(^10\)

Similar results were obtained by Kuzmina-Prigradova.\(^11\) Vagal stimulation immediately after ligation of the anterior descending branch of the left coronary artery in dogs, and even 2 to 3 days later, increased the size of the infarct together with hemorrhages and edema. Infarction after ligation of this artery could be prevented in 8 of 10 animals (monkeys, dogs, cats) by local anesthesia of the arterial wall, at the site of the ligature, with 5 per cent cocaine or 2 per cent procaine, whereas in all 9 control animals (without local anesthesia) myocardial infarction developed.\(^12\) Chronic vagal stimulation accelerated the development of electrocardiographic abnormalities in rabbits and experimental atherosclerosis produced by cholesterol feeding.\(^13\)

These results have found therapeutic application in the treatment of patients with coro-
nary heart disease by means of procaine block in the substernal mediastinum. Ostapiuk injected 60 to 80 ml. of 0.5 per cent procaine solution in 55 patients, in intervals from daily to weekly (total of 320 injections). This procedure stopped anginal attacks in 32 patients after the second injection, and in 9 there was a reduction in the frequency and severity of the attacks. Exercise tolerance increased in most patients. The electrocardiogram improved in 20 patients (disappearance of ventricular extrasystoles, less pronounced S-T depression and T inversion). Side effects of the injection (general weakness and vertigo) disappear usually after 15 to 45 minutes, but were more prolonged and severe in 5 patients. The author considered blood pressure over 200/110 or below 90/50 a contraindication to this technic. The favorable results of repeated intrathoracic procaine block were confirmed by Bulatov and Stukkei, who used for the first injection 60 to 80 ml., and for subsequent injections 100 to 120 ml. of 0.5 per cent procaine solution. No complications occurred in 219 injections in 88 patients. Only 19 patients did not show any improvement; in 36, the results were excellent (disappearance of effort angina), and a moderate improvement was noted in 33 patients. In a follow-up study of 30 patients the absence of anginal attacks lasted from 6 to 12 months in 13; from 1 to 2 years in 5; and over 2 years in 8.

These results may be considered as a basis for studies on reflex effects of stimulation of visceral receptors on coronary circulation. A variety of visceral receptors was studied, but the effect of the stimulation of gastrointestinal receptors appears to be the most important in view of the known relationship between gastrointestinal symptoms and coronary insufficiency or myocardial infarction. The previous experimental work seems to have been limited to the effect of mechanical stimulation of gastrointestinal receptors on coronary circulation.

Gastric distention produced in dogs a reflex constriction of the coronary arteries. This was confirmed by Gilbert, Fenn, and LeRoy, who measured the flow in the circumflex branch of the left coronary artery by means of a thermistromuhr after the chest was closed. A decrease of the coronary blood flow occurred in 8 of 12 animals, and was prevented by atropine.

One of the most thorough investigations on the effect of gastrointestinal stimulation has been performed by I. E. Ganelina over the past 5 years. Ganelina also started with the effect of mechanical stimulation, but rather than direct measurement of the coronary flow, electrocardiographic changes were used as criteria. Electrocardiographic changes are less specific than measurement of coronary blood flow, but have the advantage of easier application, facilitating experiments on animals on a large scale and application to man. Inflation of ligated intestinal loops up to a pressure of 40 to 80 mm. Hg produced no or only minor electrocardiographic changes in 11 normal rabbits, whereas in 9 of 40 rabbits with experimental cardiovascular pathology (arterial hypertension produced by deafferentation, atherosclerosis produced by cholesterol feeding) pronounced electrocardiographic changes occurred (mostly T inversion). Fig. 1 shows one example from Ganelina's experiments. Ganelina extended her work to chemical stimulation, which has not been studied before, and has pertinent clinical applications.

Chemical stimulation of perfused, isolated intestinal loops in situ with intact innervation with 10 to 50 gamma of acetylcholine produced in 36 normal anesthetized cats no electrocardiographic changes or a small variation of the T wave, not exceeding 1 mm. In contrast, pronounced electrocardiographic changes (abnormal T inversion, reversal of an inverted T, or ventricular bigeminy) developed in 12 of 25 cats with experimental myocarditis, produced by repeated intravenous injection of caffeine benzoate and epinephrine. The myocarditis was confirmed by autopsy. The electrocardiographic changes were prevented by prior denervation of the intestinal loop or by topical procaine application (fig. 2). It is of great interest that the heart was sensitized to mechanical or chemical stimulation of visceral receptors by cardiac pathology.
Electrocardiogram of a rabbit with experimental arterial hypertension and atherosclerosis. A, before the experiment; B, after preparation of the intestinal loop (ligation)—no essential changes; C, during inflation of the intestinal loop (80 mm. Hg.)—T wave inversion in leads II and III; D, 5 minutes after release of inflation pressure—T4 and T5 small positive, but still smaller than in “B”. (Reproduced from Ganellina,18 figure 1).

Increased sensitivity of the heart to acetylcholine stimulation of the isolated intestinal loop in situ was also shown in 7 of 11 cats with intestinal obstruction (S-T depression, flattening or inversion of T).21 In 2 dogs with experimental hypercholesteremia and probably early atherosclerosis produced by cholesterol feeding and methylthiourea over a period of several months, chemical stimulation (1/4 per cent M HCl) of an intestinal loop through a fistula produced partial inversion of T2. No inversion of T2 occurred in the same dogs before hypercholesteremia.22

Oral application of mustard in a starch capsule produced comparatively small changes of the electrocardiogram in about half of 50 healthy subjects and pronounced changes in 22 of 33 patients with coronary disease.22 The subdivision of "small" and "large" changes was arbitrary. The "large" changes include P-R prolongation over 0.04 second, changes of T in 2 or more leads over 0.5 to 0.75 mm., or S-T displacement (critical values are not given). These criteria are fairly liberal.23 The example of "large" changes in a patient with coronary heart disease (fig. 3), however, is not impressive in comparison with a positive exercise or hypoxemia test (of which Ganellina is aware), or with an abnormal meal test.24

Ganellina’s material was later enlarged to 181 subjects, including 26 normal subjects, 14 patients with arterial hypertension, 35 patients with gastrointestinal disease, and 106 patients with atherosclerosis (41 combined with arterial hypertension, and 27 combined with gastrointestinal disease). There were no sig-
significant electrocardiographic changes in 57 placebo experiments (empty starch capsules).23

"Large" changes of the electrocardiogram (as defined by the author) occurred 15 to 25 minutes after ingestion of the mustard capsule in 51 of the 106 patients with atherosclerosis, in 12 of 35 patients with gastrointestinal disease, in 4 of 14 hypertensive patients, and in 3 of the 26 control subjects. In patients with coronary heart disease, the changes occurred in the S-T segment and T wave, whereas in patients with gastrointestinal disease prolongation of the P-R interval (with or without changes of T) was more frequent. The "large" changes were less frequent in advanced coronary disease than in an earlier phase, possibly due to greater rigidity of coronary vessels. In about half of the patients with larger electrocardiographic changes after mustard ingestion, coronary artery disease was associated with gastrointestinal disorders, i.e., in 25 of the 27 patients in this group. The combination of gastrointestinal and coronary disease, therefore, increases greatly the frequency of electrocardiographic changes after mustard ingestion.

Ganelina also found a greater incidence of "large" electrocardiographic changes after mustard ingestion in patients with blood cholesterol over 200 per cent than in those below this value.18 The scatter is fairly large, but according to Ganelina, the difference in the distribution approaches statistical significance. Ganelina considered the gastric stimulation with mustard as a comparatively mild stimulus, and expected greater electrocardiographic changes with increase of the stimulus strength. Since gastrointestinal disease (gastroenteritis, food poisoning) may involve strong chemical stimulation, Ganelina analyzed the records of 486 patients with myocardial infarction hospitalized from 1945 to 1952. In 15 patients, acute gastritis or gastroenteritis was considered to be present preceding myocardial infarction. Ganelina thought that acute gas-

Figure 2
Electrocardiogram of a cat with experimental myocarditis. Leads I-III. A, before perfusion of isolated loop; B, injection of 20 gamma acetylcholine; C, 10 minutes later; D, injection of acetylcholine after preceding injection of procaine. (Reproduced from Ganelina, figure 2).
troenteritis may be the direct underlying cause in the development of the infarct. This group of 15 patients is only a small percentage of the total, but apparently rigid criteria were used in the analysis of the charts, and the number of patients with gastroenteritis preceding the infarct may well have been larger. In acute myocardial infarction, gastrointestinal symptoms were present in the majority of patients, and in one third of all cases there were data of previous gastrointestinal disease (gastritis, gastrointestinal infections, overeating, or large alcohol consumption). These results are corroborated by a case report of Prikazchikov and Petrova;25 severe coronary insufficiency with T inversion in CR₁ to CR₆ developed in a patient with intestinal arterial occlusion. Ganelina, on the basis of her experiments and clinical data, considered the presence of gastrointestinal disease in patients with coronary heart disease as a major contributing factor in the development of acute coronary insufficiency and myocardial infarction, and not merely as a symptom of it. The results stress the importance of treatment of gastrointestinal disorders, and of a proper dietary regime, in coronary artery disease.

Since meal intake includes mechanical as well as chemical gastrointestinal stimulation, the reflex mechanisms investigated by Ganelina may well be involved in the electrocardiographic changes after meals, and particularly in the abnormal response in a substantial percentage of patients with coronary artery disease. As a diagnostic test the meal test appears to be superior to Ganelina’s mustard test, because of the availability of a larger, statistically analyzed control group and the more pronounced electrocardiographic changes in a positive meal test. Ganelina, however, was primarily concerned

Figure 3
Electrocardiogram of a patient with coronary heart disease. A, basal condition; B, after ingestion of a mustard capsule flattening of T₁ and T₅, slight notching of T in CR₁, prolongation of P-R interval; C, 10 minutes later—reversal of changes. (Reproduced from Ganelina, figure 1.)

*CThe number of patients and the time of observation and not given, but probably refer to more recent material, and the prevalence of gastrointestinal symptoms in myocardial infarction corresponds to general experience.

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with the mechanism involved and its significance in coronary insufficiency and myocardial infarction.

It seems that the possibility of reflex gastrointestinal symptoms in acute myocardial infarction should also be considered, or in other words, a two-way reflex situation resulting in a vicious circle. Even if the gastrointestinal symptoms are secondary, they may well be a complicating factor in the extent or severity of the infarction or ventricular ischemia, according to Ganelina’s results.

**Sumario in Interlingua**

Ab le vaste litteratura russe relative al thema sub discussion, illustrative datos clinie e experimental es citate in supporto del these de un efecto de reflexos ab receptores gastrointestinal super insufficientia coronari.

In conclusion le autor nota le possibilitate del phenomeno contrari, i.e. de symptomas gastrointestinal como rechso de acute infarcimento myocardial.

**References**

Russian Research on the Role of Visceral Reflexes in Coronary Insufficiency
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