The interval of time elapsing between the peripheral dilatation and the cessation of pain depended somewhat on the severity of the pain. Three separate sets of observations were made on this patient, and in each case the results were the same.

In three of the 6 patients there was definite evidence that first peripheral vaso-constriction, and later a rise in arterial tension preceded the onset of pain. In 2 other cases, there was evidence only of an elevation of systemic blood pressure, but not definitely of peripheral vaso-constriction. The sixth patient refused to smoke, but exercise with a foot ergograph resulted in a rise in arterial tension with each attack of pain, but there was only slight evidence of peripheral vaso-constriction.

There are, therefore, instances of patients predisposed to *angina pectoris,* in whom cigarette smoking induces a peripheral vaso-constriction, which precedes the onset of precordial pain. At the same time an elevation of blood pressure was observed, so that it is reasonable to suppose that there was a general vaso-constriction, in which the coronary arteries may have taken part.

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Studies on Inhibition of Insulin Activity.

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(Introduced by Bela Schick.)

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In the fall of 1925 at the suggestion of Dr. Bela Schick we investigated a diabetic child with refractory periods to insulin. The study of this case led us to investigate the inhibitory effect of blood on insulin activity.

Our experiments have all been done with rabbits. Unless otherwise stated, all work was done as follows. One physiological or 3 clinical units of insulin were mixed with the substance investigated and incubated at 37° C. from 1 to 2 hours, then injected subcutaneously into rabbits, weighing 2 kilos, starved during the preceding 24 hours. Hourly blood sugar determination and clinical observations were made.

The results summarized were as follows:

2-4 cc. of human plasma caused hardly any inhibition of insulin action.

5 cc. of human plasma caused moderate inhibition of insulin action.

10 cc. of human plasma caused marked inhibition of insulin action.
15 cc. of human plasma caused complete inhibition of insulin action.
2 cc. of centrifuged unwashed blood cells caused mild inhibition.
5 cc. of centrifuged unwashed blood cells caused marked inhibition.
5 cc. of human plasma from diabetics caused almost complete inhibition.
2 cc. cells of case of myeloid leukemia caused complete inhibition.
2 cc. pus of case of empyema caused complete inhibition.

When more than one physiological unit of insulin was used, 10 cc. of plasma caused only slight—questionable inhibition. Controls of saline and insulin treated as was the plasma, etc., showed no inhibition. Likewise a few experiments with agar agar, egg albumen, and 5 cc. of horse serum (purified), treated as was the human plasma or cells, showed no inhibitory effect.

pH controls revealed that the plasma inhibited at pH 7.4 to pH 8.2 but did not inhibit at pH 6. Normal saline solution could inhibit insulin if brought to pH 9 or over by addition of NaOH. There was no difference observed whether Lilly, Squibb or Stearns insulin was used.

Inhibitions due to plasma was observed even when incubation was short (15-30 minutes), also when kept at room temperature, 20°-25° C., rather than at 37°.

Desiring to study inhibition of insulin action in infection, we followed the reaction to insulin after rabbits were injected with typhoid or staphylococcus vaccine, believing that after vaccination the reaction of the blood is like that of infection. About 50% of the animals showed moderate decreased insulin effect 3 hours after vaccine injection. This inhibitory action lasted several days in some animals. Our studies with blood from patients with high fever, serum sickness, high leucocytosis, acidosis or lipemia are too few to permit of any definite conclusions.

Our results suggest that there is something in human blood plasma which is more abundant in blood cells, more in diabetic blood than in normal human blood, and still more in leukemic cells and pus which inhibits or destroys the action of insulin. It is probably more abundant in blood of patients with fever, leucocytosis, suppurative processes, or serum sickness, than in normal state. The extent of inhibition is variable for individuals, but quantitatively proportional to the amount of blood used.

We are of the impression that the inhibitory substance may be a proteolytic enzyme, because the inhibition is greater with blood cells than with plasma, greater with leukemic cells and pus than with normal blood cells, and because it seems to be stronger during fever or infection or after vaccine injection. Even more significant, in

that it may be enzyme action, is the experiment in which the plasma or pus heated at 57° for 1 to 2 hours no longer inhibited insulin action. Similar experiments with blood cells were not as convincing as was plasma or pus.

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Standardization of Liver Extract.

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When rabbits are injected intranarrowly with *B. welchii* toxins according to the Torrey-Kahn[1] technique, they rapidly become anemic and exhibit many of the characteristic blood changes described in reports of pernicious anemia in man.

There is a rapid decrease in the number of red cells (for 5 rabbits: 31, 32, 38, 38, 41%) and in hemoglobin content (for 5 rabbits: 29, 30, 30, 31, 37%), the lowest values being reached between the fifth and tenth days. Following this, there is a compensatory period of 10 to 15 days during which time the experimental animals show definite increase in the number of red cells and hemoglobin. Beginning with about the thirtieth day after injection of the toxin, the experimental animals show a progressive decrease in the number of red cells and in the hemoglobin content.

If an aqueous solution of liver extract is given by stomach tube to these anemic rabbits while they are at the lowest point in red count and hemoglobin (about the fifteenth day), there is a definite increase in each. This is, however, the period in which the animals are making a strong effort to compensate for the injury to the hematopoietic system and one does not obtain such striking results as when liver extract is given in the stage of progressive decline (35 days, or later).

There can be no doubt as to the beneficial effects of liver extract in this type of experimental anemia. Our results with some 20 animals indicated a rough proportionality between the amount of liver extract given and the increase in the number of red cells and in

[1] A paper by John C. Torrey and Morton C. Kahn, "Progressive Effects of a Single Intra-tibial Injection of *B. welchii* Toxins," read at the joint meeting of the American Association of Pathologists and Bacteriologists and the American Association of Immunology, Washington, D. C., May 1st, 1928. We are greatly indebted to Drs. Torrey and Kahn for many suggestions.